THE

AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JANUARY, 1943

ORIGINAL ARTICLES

THE ADMINISTRATION OF SULFONAMIDE MICRO-CRYSTALS BY INHALATION*

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The usefulness of the sulfonamides has been limited by their low solubility in water. For parenteral administration the water solubility is so low that an effective dose of the drug requires large volumes of solution. The sodium salts of the sulfonamides, on the other hand, are more soluble in water, but their extreme alkalinity limits their use in parenteral injection or application to mucous membranes.[4] There are some exceptions to these limits of usefulness,[3,5,6] but any form of the drugs which could increase their possible modes of administration would obviously be valuable.

Recently Chambers and his associates[2] developed a method for producing aqueous preparations of the sulfonamides which are neutral in reaction, yet adequately concentrated. They prepared minute crystals, "micro-crystals," of these drugs, which form a stable aqueous suspension resembling milk of magnesia in physical properties. This preparation can be injected through fine hypodermic needles, poured into the interstices of wounds or sprayed to form a sulfonamide "fog" in the air. Experiments on the use of this micro-crystal suspension in wounds have been reported elsewhere.[1] This paper is concerned with the administration of sulfonamides by inhalation, by introducing sulfonamide smoke into the air.

* Aided by a grant from the Smith, Kline & French Laboratories, Philadelphia.

Method. The sulfathiazole "smoke" used in these experiments was derived from a 5% aqueous suspension of sulfathiazole micro-crystals.* The suspension was introduced into an atomizer supplied with compressed air which produced a finely divided spray. The resultant spray was led into a chamber containing Swiss white mice weighing about 20 gm. In this chamber the droplets quickly dried, leaving the sulfathiazole "smoke" in the air. Most of the particles of sulfathiazole in air were about 1.6 to 4.8 micra in diameter. Larger crystals were also found.

Pharmacologic Experiments. A number of experiments were performed to determine the effect on normal mice of prolonged inhalation of such "smoke." Groups of mice were placed for different lengths of time in a chamber containing the sulfathiazole smoke and were examined at various intervals thereafter.

The mice were examined for general ill effects and for any gross changes in the lungs. Analyses for sulfonamide concentration in the blood and for total sulfonamide content of the lungs and stomach were carried out.

TABLE 1.—THE SULFONAMIDE CONCENTRATION OR CONTENT IN BLOOD, LUNG AND STOMACH AFTER INHALATION OF SULFATHIAZOLE SMOKE

Length of exposure	Time after end of exposure	Blood, mg./100 cc.	Lung contents, mg.	Stomach contents, mg.
15 min.	0	1.91	0.0033	0.055
	0	1.45	0.0027	
30 min.	0	5.87	0.0086	0.037
	0	3.17	0.0049	
30 min.	30 min.	1.98	0.0030	
	30 min.	3.56	0.0037	
30 min.	1 hour	2.19	0.0027	
	1 hour	2.11	0.0027	
1 hour	0	2.38	0.0086	0.223
	0	5.08	0.0093	0.180
1 hour	1 hour	3.50	0.0046	
	1 hour	2.90	0.0030	
1 hour	4 hours	4.03	0.0063	
	4 hours	1.25	0.0040	
1 hour	8 hours	1.65		
	8 hours	1.58		
2 hours	0	2.97	0.0066	
	0	1.65	0	
2 hours	1 hour	1.78	0.0037	
	1 hour	4.88	0.0073	
2 hours	2 hours	7.00	0.0076	
	2 hours	3.89	0.0053	
2 hours	4 hours	2.11	0.0040	
	4 hours	6.79	0.0033	
4 hours	0	15.18		
	0	11.55		
4 hours	1 hour	16.57		
	1 hour	13.27		
4 hours	2 hours	4.09		
	2 hours	5.21		
4 hours	4 hours	2.84		
	4 hours	2.05		
4 hours	8 hours	0.59	...	0.286
	8 hours	1.98		

*This material was supplied by the Smith, Kline & French Laboratories, Philadelphia.

No general ill effects were observed in the mice during or after the inhalation of the sulfathiazole smoke and gross examination of the lungs at different intervals up to several days after the inhalation revealed no changes except for mild hyperemia soon after the inhalation.

Typical results of the analyses for sulfonamide are shown in Table 1.

In order to determine whether significant amounts of sulfathiazole can be absorbed from the lungs, tracheotomy and ligation of the esophagus were performed on guinea pigs and the tracheotomy tube was exposed to the spray. Control guinea pigs were exposed to sulfathiazole spray in a chamber. The results of this experiment are shown in Table 2.

TABLE 2.—BLOOD SULFATHIAZOLE CONCENTRATIONS IN NORMAL AND TRACHEOTOMIZED GUINEA PIGS

Tracheotomized	Normal
Pig 1.—3.46 mg./100 cc.	3.89 mg./100 cc.
Pig 2.—1.93 mg./100 cc.	

Finally, to indicate whether the blood levels attained in normal mice exposed to the smoke were due primarily to pulmonary or gastro-intestinal absorption, sulfathiazole was administered by gavage to normal mice and its effect on the blood level determined. It was found that 10 mg. of sulfathiazole placed in the stomach gave rise to a blood concentration of 12–13 mg./100 cc.; and 5 mg. in the stomach, to a maximum level of 4–5 mg./100 cc. Amounts of sulfathiazole such as those found in the stomachs of our mice could not then be considered of major importance in the blood levels observed since the gastric contents never exceeded 0.25 mg. following inhalation of the smoke.

As a control on the particular usefulness of the micro-crystals for sulfathiazole inhalation, mice were exposed to a spray of sodium sulfathiazole solution under similar circumstances. All these mice died within a few hours, their lungs showing grossly an extreme hyperemia.

Chemotherapeutic Experiments. An interesting and possibly important direction for testing the particular value of the inhalation route of administration of the drug was indicated by the experiments of Wells and Henle.[7]

It is known that mice are strongly resistant to inhaled pneumococci, and can breathe air heavily contaminated with these bacteria without ill effects. These authors found, however, that if mice had previously inhaled sublethal doses of influenza virus they would become more susceptible to inhaled pneumococci, and would often develop fatal pneumonia.

If this could be interpreted as a decrease in resistance of the lung to pneumococci, then one could suspect an analogy to a number

of situations in human medicine. An increase in likelihood of secondary bacterial pneumonia complicates a number of important infections and toxic states.

Accordingly, experiments were undertaken to evaluate the effectiveness of sulfathiazole smoke in secondary bacterial pneumonia of mice. Preliminary experiments were done to determine the optimal relations among the factors involved. It was found that a spray of a 1 : 500 dilution of influenza A virus egg fluid (Strain P2) was barely sublethal. Moreover, if mice exposed to this spray were exposed to a spray of pneumococcus broth culture 6 days later, 70 to 80% of them would die of pneumonia in a few days. Normal mice showed no ill effects from exposure to the same spray of pneumococci.

These factors were optimal in that they produced the most striking difference in mortality rate between normal mice and mice previously exposed to air-borne influenza virus; *i. e.*, the most striking evidence of decreased resistance to air-borne pneumococci. Experiments were then carried out to determine whether the smoke of micro-sulfathiazole could prevent the secondary bacterial invasion in mice following a primary sublethal infection with the influenza virus. Exposure to the sulfathiazole smoke lasted 2 to 3 hours, 4 times a day for 3 days starting with a period 2 hours prior to inhalation of the pneumococci. Six days after exposure to the pneumococci, the mice were sacrificed, the lungs examined grossly and lungs and heart's blood subcultured and examined for pneumococci. Table 3 illustrates the results from a typical experiment.

It is, of course, known that orally-administered sulfathiazole

TABLE 3.—THE EFFECT OF SULFATHIAZOLE INHALATION ON INFLUENZAL MICE EXPOSED TO PNEUMOCOCCI.

	Observations on each mouse; groups of 10									
	1	2	3	4	5	6	7	8	9	10
Influenza virus alone	D13 (x)	D13 (4)	(1)	(1)	0	0	0	0	0	0
Pneumococcus control	0	0	0	0	0	0	0	0	0	0
Influenza virus + pneumococcus	D9* (4)	D9* (4)	D9* (4)	D9* (3)	D9* (3)	D9* (3)	D10 (x)	D11* (4)	0	0
Influenza virus + pneumococcus, + sulfathiazole inhalation . .	D11* (4)	(4)	(3)	(3)	0	0	0	0	0	0

D9, died on 9th day, etc. (1), (2), (3), (4) indicate severity of lung lesions. (x), could not be examined. 0, no lesion.

* Pneumococcus Type I recovered from lungs and/or heart's blood.

TABLE 4.—THE EFFECT OF SULFATHIAZOLE ADMINISTERED BY GASTRIC GAVAGE ON INFLUENZAL MICE EXPOSED TO PNEUMOCOCCI

	Observations on each mouse; groups of 10									
	1	2	3	4	5	6	7	8	9	10
Influenza virus control .	(3)	(3)	(3)	(2)	(2)	(2)	(2)	0	0	0
Pneumococcus control .	0	0	0	0	0	0	0	0	0	0
Influenza virus + pneumococcus	D9*	D10*	D10*	D11x	D12*	D12*	D12x	(3)°	(2)°	0
Influenza virus + pneumococcus + sulfathiazole	(3)	(3)	(3)	(2)	(2)	(2)	(1)	(1)	0	0

D9, died on 9th day, etc. (1), (2), (3), (4) indicate severity of lung lesions. (x), could not be examined. 0, no lesion. (°) indicates negative culture.

* Pneumococcus Type I recovered from lungs and/or heart's blood.

can markedly reduce the mortality of pneumonia, and as a control we repeated the experiment shown in Table 3 substituting gastric gavage of micro-sulfathiazole suspension for the inhalation. It was found that this secondary pneumonia could be successfully treated with oral sulfathiazole, provided a sufficiently high blood-level were maintained. The results of such an experiment are shown in Table 4.

Discussion. The pharmacologic experiments show that sulfathiazole can be administered by inhalation and that high blood levels can be attained in this manner. There is also considerable evidence that the blood concentration is due to absorption from the lung rather than from the stomach.

The very low amounts of drug found in the lung are of interest, since they indicate a very rapid solution into the blood stream of the crystals inhaled in the smoke. The mild hyperemia and the rather quick rise in blood level during the first hour of exposure are consistent with this interpretation. The presence of minute crystals of drug may well be a sufficient irritant to stimulate such hyperemia.

Wide differences are found between the blood levels of different mice exposed under presumably similar conditions, but these are very probably due to technical difficulties. First, the chambers used thus far have been small ones without circulating devices, and the air stream from the spray is fairly forceful (15 to 26 pounds per square inch). These mechanical factors probably produce great differences in air-concentration of the drug throughout the chamber. Secondly, the mice tend to collect in heaps, partly to avoid the direct air stream. The fur of uppermost mice probably filters out some of the drug from the air to be inhaled by those below. Work is under way now to resolve these technical difficulties.

The chemotherapeutic results are at the present writing very stimulating. We have shown that the inhalation of sulfathiazole smoke can strikingly reduce the mortality of secondary pneumonia induced by a state of decreased resistance to the pneumococcus. There is some reason to suspect that the amounts of drug administered were a good deal higher than the threshold value. However, a sufficiently high blood concentration of sulfathiazole attained by other means can accomplish the same result.

In the purely therapeutic sense, then, no qualitative superiority of the pulmonary over the oral route has been demonstrated thus far, and any quantitative difference is yet to be investigated.

As to possible prophylactic effects, however, the investigation of any qualitative difference between the two modes of administration seems well worth while. With respect to practical applications to human medicine* it would be well to know whether either method

* Dr. Chapple has kindly made us a simple insufflator, operated with an atomizer bulb, which easily introduces the dry micro-crystals as "smoke" into nasal or oral cavities in sufficient amounts to affect rhinitis or pharyngitis locally as well as producing satisfactory sulfonamide blood levels. We hope that he will report on this aspect shortly.—Ed.

can prevent pneumonia to the exclusion of the other method, since prevention is, of course, far preferable to any decrease of mortality of pneumonia itself. And theoretically, it would be of interest to determine whether direct application of sulfathiazole to the lung can increase its effective resistance by any local mechanism.

Summary. A technique is described for producing a "smoke" of sulfonamides in air by spraying a suspension of minute crystals.

Mice inhaling sulfonamide smoke develop high blood concentrations of the drug.

This method of administration can be used to reduce greatly the mortality due to inhalation of pneumococcus in mice suffering with influenza.

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MEDICATION BY CHEWING SULFADIAZINE AND OTHER DRUGS INCORPORATED IN A PARAFFIN BASE

A Preliminary Report

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The incorporation of acetylsalicylic acid, pepsin, phenolphthalein and flavoring agents in chewing gum is too well known to require comment. Paraffin, on the other hand, has not, as far as I have been able to determine, been employed in this manner; though the chewing of pure paraffin to promote salivary secretion has been recommended in the treatment of bleeding peptic ulcer. If drugs incorporated in paraffin are slowly released in the saliva when chewed and if, in the process of chewing and swallowing, they come into intimate contact with the gums, pharynx and esophagus, possibilities for more effective treatment of gingivitis, stomatitis, pharyngitis, and esophagitis by this means may be opened. The present study suggests that such is the case.

Fifteen milligrams ($\frac{1}{4}$ gr.) of gentian violet and later 0.3 gm. (5 gr.) of methylene blue were incorporated with 1 gm. (15 gr.) of paraffin* and were given to 13 subjects to chew. Observations as to the extent and degree of mucosal staining were made by Drs. O. C. Hirst and J. A. Bertolet, chiefs of services at the Episcopal Hospital.

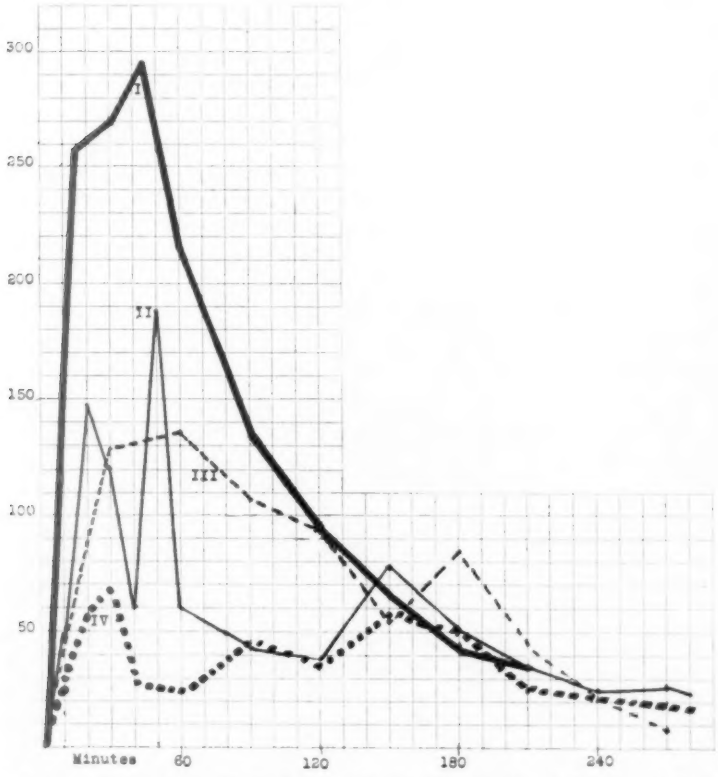

CHART 1.—Level of sulfadiazine in saliva during chewing of 0.3 gm. of the drug incorporated in 1 gm. of paraffin in 4 cases. Blood sulfadiazine levels at the end of Cases 2 and 4, respectively, were 1.2 mg. and less than 0.8 mg. per 100 cc.

Results. It was found that the dyes stained the tongue and gingival margins deeply; that next in intensity the remaining buccal

* Paraffin having a melting-point of 50° to 52° C., such as is used in embedding pathologic material, is used in cold weather; ordinary paraffin such as is sold at grocery stores for putting up jellies is satisfactory only in summer. In either case the paraffin should be warmed in the mouth before being chewed.

The sulfadiazine paraffin cubes, at present used by me, are furnished through the kindness of Lederle Laboratories, Inc., Pearl River, N. Y.

mucosa was stained; that the degree and extent of staining of the mucous membrane back of the anterior pillars and soft palate depended largely upon the position assumed by the patient while chewing and swallowing. The tonsils and posterior pharynx were usually not stained if the patient assumed the upright position during the experiment; but with the subject chewing and swallowing in the recumbent position with the head lower than the shoulders, the tonsils and posterior pharynx usually became definitely stained. The stained area varied, but in no case did the dye reach to the true vocal cords, the eustachian tube orifices or the spheno-ethmoidal area. Usually it was limited to the structures in close proximity to the oral cavity, including the tonsils and posterior pharyngeal wall. This was interpreted as indicating the possibility of securing maximum local action upon the gums, tongue and buccal mucosa, and action to a lesser degree upon the oropharynx from the chewing of medicated paraffin. Action upon the esophagus was taken for granted.

The next step involved the matter of dosage. Eleven subjects were given paraffin containing from 0.065 gm. (1 gr.) to 0.3 gm. (5 gr.) of sulfadiazine to chew, and serial salivary sulfadiazine determinations were made by Miss N. M. Catena, B.S., M.T. (A.S.C.P.). It was found that 0.3 gm. (5 gr.) of the drug was the most satisfactory amount to incorporate in the paraffin. Four of the resulting curves are shown in Chart 1. It will be seen that salivary sulfadiazine levels ranging from 33 to 96 mg. per 100 cc. of saliva (average, 66.5 mg.) result from chewing this dose for 2 hours. At the end of 3 hours the levels ranged from 42 to 84 mg. per 100 cc. of saliva (average, 56.7 mg.). Considering the fact that sulfadiazine blood levels of between 5 and 15 mg. per 100 cc. of blood are generally regarded as satisfactory in the treatment of pneumonia and that levels of 20 to 25 mg. per 100 cc. were found after 4 hours in the saliva, it was thought that the above salivary levels were sufficiently high to be useful locally. The findings indicate that a therapeutic trial of the drug in this dosage is justified, the medicated paraffin sticks being given to patients with directions to chew until the next meal and then discard. Two or three chews per minute is sufficient. The material is left in the mouth throughout the night. The paraffin is, of course, quite harmless if swallowed. This method of treatment is being tried on a series of cases of tonsillitis and pharyngitis, the results to be reported in a later paper. Neoarsphenamine incorporated in paraffin has also been used in the treatment of Vincent's infection of the gums and tonsils, and sodium bicarbonate incorporated in paraffin in the treatment of pyrosis.

Summary. The incorporation of various drugs in a paraffin base to be chewed offers a means of prolonged medication of the mouth, pharynx and upper gastro-intestinal tract.

THE EFFECT OF IRON ON THE HEMOGLOBIN REGENERATION IN BLOOD DONORS

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The present great demand for donors to supply blood and serum for transfusions makes it important to know how rapidly the hemoglobin returns to its normal level, how frequently blood may be taken from an individual with safety, and the advisability of therapy to hasten hemoglobin regeneration. A majority of the previous reports on this subject have only shown that professional donors are able to give repeated donations within a space of a few months without developing anemia. Snapper, Liu, Chung and Yu[3] reporting on a group of Chinese donors found that hypochromic anemia occasionally developed in those who subsisted on an inadequate diet and that the administration of iron aided in alleviating their anemia. Santy[7] also has shown that ferrous sulfate increased the rate of hemoglobin regeneration in 27 blood donors to whom it was administered. With 12 gr. of ferrous sulfate per day, he found the regeneration to be 8 times as fast as without iron and concluded that it was best to begin the administration of iron before the blood donation was made so as to build up an iron reserve to compensate for the expected blood loss.

In a previous communication[4] we presented some of the data acquired from a study of 200 blood donors who had given a total of 636 donations and showed that the average time required for the hemoglobin to return to its original level was 49.6 days when 500 to 600 cc. of blood was withdrawn, and that hemoglobin was regenerated at a rate of 0.0495 gm. per 100 cc. of blood per day under these circumstances. A majority of the subjects, 74.2%, had returned to their original hemoglobin level at the end of 8 weeks, but 25.8% required a longer recovery period, up to 15 weeks. When an iron salt was administered to a group of 89 of these donors after their second blood donation it was found that the rate of hemoglobin regeneration was increased by 49% so that the average daily hemoglobin increase per 100 cc. of blood was 0.0772 gm. and the recovery period was shortened to 35.2 days. Under these conditions it was found that 93.5 of the subjects had regained their normal hemoglobin level at the end of 8 weeks. Iron therapy was administered continuously and some of these subjects gave as many as 5 dona-

tions, subsequent donations being given as soon as their normal hemoglobin level had been reached. It was found that in spite of the continuous iron therapy there was a gradual decline in the rate of hemoglobin formation after each donation until it was being formed at a rate which was no more rapid than it had been without iron therapy. It seemed, therefore, as if iron had progressively less effect with its continuous administration. In Table 1 is shown the decline in the average daily hemoglobin regeneration in these subjects after repeated donations. If iron were acting only to replace an iron deficiency it would seem that its effect should remain constant, since previous work[1] has shown that the dose of iron which was administered (iron and ammonium citrates 1 gm. per day) is sufficiently large to be effective in iron deficiency anemias. Balance studies[5] have shown that from this amount of iron and ammonium citrates 53.7 mg. of iron per day are retained in the body, whereas the regeneration of 0.0772 gm. of hemoglobin per 100 cc. of blood per day would require only 12.9 mg. of iron in an individual with a blood volume of 5000 cc. The size of the dose would not appear to be a factor in the gradual lessening in the hemoglobin response.

TABLE 1.—AVERAGE DAILY HEMOGLOBIN REGENERATION WITH AND WITHOUT IRON THERAPY

(Gm. hemoglobin per 100 cc. blood per day)

Donation		No. of cases				
		155	83	31	12	11
1	No therapy	.050	.052	.055	.055	.055
2	Continuous iron therapy	..	.077	.087	.101	.101
3	Continuous iron therapy	..	..	.069	.072	.071
4	Continuous iron therapy	..	..	..	.049	.049
5	Continuous iron therapy	..	..	..	..	.058

Iron was administered to groups of these blood donors in alternating periods with therapy interspersed with recovery periods during which no medication was given. The subjects for this investigation were predominantly medical students, the resident staff, and hospital employees and the data presented here are exclusively on male donors. Hemoglobin and hematocrit determinations were made before the blood donation, 24 hours after the donation and at weekly intervals thereafter until the blood hemoglobin had returned to its normal level. From these data were determined the length of time required for the hemoglobin to return to normal, the weekly gain in hemoglobin, and the average daily hemoglobin increase per 100 cc. of blood. The methods and procedures employed were the same as described in the previous communication.[4]

In Table 2 is shown the average daily hemoglobin regeneration in 2 groups of subjects. In the first group are the results in 4 subjects who gave 1 blood donation without iron therapy and 6 subsequent

donations while receiving continuous iron therapy. The second group shows the results in 2 subjects who gave 9 subsequent donations while receiving therapy. It will be noted that there is a marked increase in the rate of hemoglobin formation during the first recovery period on iron therapy but a gradual decline thereafter except for a secondary increase during the 5th period on iron therapy which is again followed by a slowing in the rate of regeneration.

TABLE 2.—AVERAGE DAILY HEMOGLOBIN REGENERATION
(Gm. hemoglobin per 100 cc. blood per day)

Donation		No. of cases 4	2
1	No therapy	.051	.045
2	Continuous iron therapy	.123	.113
3	Continuous iron therapy	.059	.064
4	Continuous iron therapy	.059	.059
5	Continuous iron therapy	.044	.053
6	Continuous iron therapy	.093	.105
7	Continuous iron therapy	.043	.056
8	Continuous iron therapy	..	.046
9	Continuous iron therapy	..	.054
10	Continuous iron therapy	..	.076

TABLE 3.—INDIVIDUAL RECORDS OF AVERAGE DAILY HEMOGLOBIN REGENERATION
(Gm. hemoglobin per 100 cc. blood per day)

Donation		Subject 1	2	3	4	5	6
1	No therapy	.058	.072	.044	.072	.030	.059
2	Continuous iron therapy	.130	.134	.140	.123	.129	.098
3	Continuous iron therapy	.114	.044	.044	.064	.059	.068
4	Continuous iron therapy	.094	.025	.061	.058	.079	.039
5	Continuous iron therapy	.043	.134	.034	.038	.043	.062
6	Continuous iron therapy	.035	.042	.088	.076	.161	.048
7	Continuous iron therapy	..	..	.033	.029	.065	.046
8	Continuous iron therapy	..	..	..	..	.048	.043
9	Continuous iron therapy	..	..	..	..	.040	.069
10	Continuous iron therapy	..	..	..	..	.084	.068
11	Continuous iron therapy	..	..	..	..	..	.063
12	Continuous iron therapy	..	..	..	..	..	.090
13	Continuous iron therapy	..	..	..	..	..	.028
14	Continuous iron therapy	..	..	..	..	..	.041
15	Continuous iron therapy	..	..	..	..	..	.157

The same feature is brought out in Table 3 in which are presented individual records of 6 subjects who were similarly treated with the continuous administration of iron after recovery from the first blood donation. In each instance the first period on iron therapy is characterized by a marked increase in the rate of hemoglobin regeneration but a slower rate prevails after subsequent donations. There is, in individual cases, considerable variation from one period to another but except for Case 1 each shows at least one subsequent period in which there is a definite secondary increase in hemoglobin regeneration. This appears during the 4th or 5th period on iron therapy in Cases 2, 3, 4, and 5, while in Case 6 there is an accelerated regeneration in the 11th and 14th periods while on iron therapy.

It is impossible to say whether or not the iron therapy is responsible for this acceleration in the later periods. In cases which were followed through 4 postdonation periods without iron therapy there was a moderate increase in hemoglobin formation in the 4th period but the change was not marked. From these data there is no evidence of a permanent lessening of the hemoglobin regenerative power as the rate of production does not drop significantly or consistently below the rate which prevailed before iron therapy was begun so that repeated donations of blood may be made without evident harm to the individual as far as hemoglobin formation is concerned. It is also apparent that iron therapy does not exert a sustained effect on hemoglobin regeneration.

TABLE 4.—AVERAGE DAILY HEMOGLOBIN INCREASE IN GROUPS RECEIVING AND NOT RECEIVING IRON THERAPY

(Gm. hemoglobin per 100 cc. blood per day)

		No. of cases			
Donation		33	13	8	2
1	No therapy	.055	.054	.053	.061
2	Iron therapy	.073	.087	.088	.121
3	No therapy	.056	.061	.063	.070
4	Iron therapy	..	.079	.073	.072
5	No therapy	..	..	.065	.057
6	No therapy	..	..	..	.024

In Table 4 is shown the average daily hemoglobin increase in groups of donors to whom iron was administered after alternate donations and withheld after the others. It will be noted that the usual increased rate of hemoglobin formation was present during the first period of iron administration, but that the subsequent administration of iron, while causing an increase as compared to the preceding period, did not produce as great a response as was obtained with its first administration of iron. In those periods during which no medication was given it is seen that the rate of hemoglobin regeneration decreases as compared to the preceding periods with iron therapy, but it will be noted that the rate does not drop to the level of the first donation. It appears therefore that the effect of the iron previously administered is carried over into the subsequent period. This is the type of response that would be anticipated from previous studies on the effect of iron therapy on hemoglobin formation in which it was shown that there is a peak in the rate of hemoglobin regeneration which is followed by a decreased regenerative rate even though iron is administered continuously.[3] Since the rate of hemoglobin regeneration during the periods without iron does not drop below the original control level it does not seem that the lessened effect of subsequent iron therapy can be explained on the basis of bone marrow exhaustion. It is rather on the basis of a lessened effect of iron itself on hemoglobin production.

In Table 5 are the results obtained in subjects who received no therapy after their first donation, iron therapy during 2 subsequent

postdonation periods and then no therapy after the following donations. In the 1st period of iron therapy a marked increase was noted; during the 2d period of iron therapy the response was less marked, and then with no therapy the rate of regeneration dropped markedly. This illustrates the fact that even with the giving of iron for a longer period of time and the storage of larger amounts of iron in the tissues during 2 periods of therapy there is still a sharp drop in the rate of hemoglobin regeneration when the medication is discontinued. Although adequate reserves are built up during the preceding periods of therapy, the regeneration of hemoglobin drops with the discontinuance of iron. This drop is no greater than occurred in the corresponding period shown in Table 1 when iron was given continuously so that the decreased rate cannot be laid directly to the withholding of iron. This comparable drop in the rate of hemoglobin regeneration which occurred in corresponding postdonation periods regardless of whether iron is given continuously (Table 1) or discontinued (Table 5) corresponds to the results obtained in mild anemia. To one group of anemias iron was given continuously and to a second group it was given for 60 days and then discontinued.[3] The resultant curve of hemoglobin regeneration was similar in both groups and corresponds to the results observed in these blood donors.

TABLE 5.—RESULTS OF THERAPY ADMINISTRATION ACCORDING TO PERIODS
(Gm. hemoglobin per 100 cc. blood per day)

		No. of cases	
Donation		7	4
1	No therapy	.047	.050
2	Iron therapy	.082	.092
3	Iron therapy	.069	.077
4	No therapy	.041	.047
5	Iron therapy	..	.059

It will also be noted in Table 5 that the subsequent administration of iron after one period without the medication failed to produce as great a response as was previously obtained. There is a slight response, however, which is more evident when compared to the results shown in Table 6 where iron was withheld for 2 periods. In Table 5, Period 5, iron was given, while in Table 6, Period 5, it was withheld. With iron therapy during this corresponding period there is a definite increase which is not true when iron was withheld.

In Table 7 the subjects received no iron for the first 2 periods during which the rate of regeneration remained about constant whereas with iron therapy in the 3d postdonation period the usual marked increase occurred. This is further evidence that the results are due to iron rather than to a stimulation resulting from the loss of blood, since in the previous tables iron was given in the 2d period and the rate of regeneration increased with this medication. In the present group, Period 2 was passed without medication and

without change in hemoglobin formation, whereas the giving of iron in Period 3 produced the expected increase. Withholding iron in Period 4 led to a prompt reduction in hemoglobin formation.

TABLE 6.—RESULTS OF THERAPY ADMINISTRATION ACCORDING TO PERIODS
(Gm. hemoglobin per 100 cc. blood per day)

Donation		No. of cases 2
1	No therapy	.043
2	Iron therapy	.072
3	Iron therapy	.049
4	No therapy	.051
5	No therapy	.027

TABLE 7.—RESULTS OF THERAPY ADMINISTRATION ACCORDING TO PERIODS
(Gm. hemoglobin per 100 cc. blood per day)

Donation		No. of cases 7	4
1	No therapy	.056	.059
2	No therapy	.052	.060
3	Iron therapy	.082	.092
4	No therapy	..	.049

TABLE 8.—RESULTS OF THERAPY ADMINISTRATION ACCORDING TO PERIODS
(Gm. hemoglobin per 100 cc. blood per day)

Donation		No. of cases 11	5	3	2
1	Iron therapy	.068	.072	.076	.072
2	No therapy	.046	.054	.062	.069
3	Iron therapy	..	.057	.055	.063
4	No therapy	..	..	.035	.030
5	Iron therapy	..	..	..	.067

In Table 8 the iron is given in alternate periods except that it was administered after the 1st donation and withheld after the 2d, and the alternate giving and withholding of iron continued on this schedule. The results are the same as previously commented upon, *i. e.*, an increased rate of hemoglobin regeneration with iron, a diminished rate without it. In the 3d period there is no response to iron although it had been effective after the first donation.

Comment. From these results it is evident that the administration of iron to blood donors hastens the regeneration of hemoglobin and shortens the recovery period. If the drug is given continuously, and repeated blood donations are given, the effect of iron becomes less marked during the 2d recovery period and has no effect on the rate of hemoglobin regeneration during subsequent recovery periods. In most individuals who give many donations while on continuous iron therapy there is a secondary and late increase in hemoglobin regeneration after 5 to 6 donations have been given, but this is usually not as great as the first response that was obtained. On the whole there is a gradually decreasing effect from iron therapy.

The reason for the increased rate of production of hemoglobin with iron therapy is not obvious for there is no evidence of depleted

iron stores in these individuals. If it were purely a matter of replacement therapy or making iron more available, there should not be a decreasing therapeutic effect as the iron reserves become better filled with its prolonged administration. It has previously been shown that iron is retained by the body from this dosage of iron and ammonium citrates and that the storage continues over a long time.[2] The availability of iron and the amount of iron reserves in the body do not apparently play a part in this effect. If the results were due to an elevation in the blood serum iron[6] it should still be effective after the long periods of iron administration, since the serum iron level should increase during the 4th and 5th postdonation periods as well as in the 1st period. The increased hemoglobin response does not seem to be logically explained on the elevated serum iron level or the iron stores of the body.

When the administration of iron is discontinued after it has been given during one or more postdonation periods there is a sharp reduction in the regenerative rate although it is maintained somewhat above the rate prevailing during the control period which was without therapy. This shows some latent action of the iron which cannot be due entirely to the serum iron level. Since the iron stores are well filled these should maintain the rate of hemoglobin regeneration at a high level but since they do not maintain this level the state of the iron reserves are obviously not playing the most important rôle.

After the rate of regeneration has once been increased by iron and then allowed to return to the normal during a period without iron, subsequent administration of iron has less effect and does not again increase the regeneration rate to the high point obtained with the first iron administration.

These features suggest that iron has a stimulating effect on hemoglobin formation which is not dependent upon changes in the level of the iron in the blood serum, the reserve supply of iron, or the availability of the iron. They are in agreement with previous findings which we have reported and which we have interpreted as evidences of stimulation.

Conclusions. The administration of iron to blood donors hastens the regeneration of hemoglobin, but the effect of iron therapy is transient. Iron therapy given after subsequent blood donations does not cause as great an acceleration as with its first administration.

Iron apparently has a stimulating effect on hemoglobin formation as well as acting as replacement therapy.

There is no evidence of bone marrow exhaustion after repeated donations.

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THE CLOTTING ACTION OF FER-DE-LANCE VENOM

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Introduction. The use of snake venom as a local styptic was suggested because of its well known clotting action. Eagle[3] described the coagulating effect of various snake venoms and found that the venom of the fer-de-lance snake (Bothrops atrox) acted as an enzyme in converting prothrombin to thrombin and fibrinogen to fibrin. The fer-de-lance venom contains, in addition to the clotting factor, powerful hemorrhagins and neurotoxins which restrict its use. In 1939, a "detoxified" product became available which manifested great clotting ability but less hemolytic and neurotoxic effects. As the experiments to be reported will show, the term "detoxified" does not mean that the venom was non-toxic.

A study of the action of this "detoxified" venom was undertaken by us in order to determine its possible use parenterally in hemorrhagic conditions. Observations were made on its effect on whole blood and on fibrinogen solution *in vitro* and on its action after parenteral injection in rabbits and dogs.

Material and Methods. The stock venom was the crude dried venom of the fer-de-lance snake. The "detoxified" venom was the product obtained by evaporation of the aqueous supernate after a 1% solution of stock venom had been shaken with an equal volume of chloroform for 48 hours. Venom dilutions were made up in 0.85% solution of NaCl. The clotting time of rabbits was measured by the capillary tube method and that of dogs by a modification of the 8 mm. tube method. The *in vitro* experiments were performed on both oxalated and heparinized normal human and normal dog blood. Blood was kept fluid indefinitely by the addition of 1 cc. of N/10 sodium oxalate solution to 9 cc. of whole blood or by the addition of 300 units* of heparin (Liquæmin, Roche-Organon) to 10 cc.

* One anticoagulant unit is the anticoagulant power necessary to keep 1 cc. of recalcified, citrated beef plasma liquid for 4 hours at 37° C.

of whole blood. Dog fibrinogen, obtained through the courtesy of Dr. Wm. De W. Andrus, was prepared according to the method of Warner, Brinkhous and Smith.[11] A Summerson[10] photo-electric colorimeter was used to measure the turbidity of the fibrinogen-venom solutions. Prothrombin determinations were made by the method of Warner, Brinkhous and Smith[11] and fibrinogen was measured by the method of Bancroft, Stanley-Brown and Quick.[1]

Experiments and Results. A. *In Vitro Experiments. Clotting Effect of Venom on Whole Blood:* The clotting effect of *B. atrox* venom on whole blood is shown in Table 1. Serial dilutions of both stock and "detoxified" venom were made. One-tenth cc. of each dilution was added to 1 cc. each of oxalated and heparinized whole blood. The time required for the formation of an invertible, self-supporting clot is tabulated. In any given dilution, stock venom was a more rapid clotting agent than "detoxified" venom. Heparinized blood was clotted less rapidly than oxalated blood. Lysis of the clots resulted in the presence of the higher concentrations of the venom. Stock venom in 1:4000 dilution completely lysed the clot in 6 hours; whereas "detoxified" venom in 1:1000 dilution only caused partial lysis in 24 hours.

TABLE 1.—CLOTTING TIME OF OXALATED AND HEPARINIZED DOGS' BLOOD AFTER THE ADDITION OF FER-DE-LANCE VENOM

Final dilution, venom in blood	Clotting time	
	Oxal. blood	Hep. blood
A. Stock Venom		
1:1000	0′ 05″	0′ 13″
1:2000	0′ 10″	0′ 17″
1:4000	0′ 11″	0′ 15″
1:8000	0′ 17″	0′ 22″
1:16000	0′ 21″	0′ 32″
1:32000	0′ 26″	1′ 31″
1:64000	0′ 32″	2′ 17″
1:128000	0′ 55″	5′ 42″
1:256000	3′ 32″	13′ 40″
1:512000	5′ 40″	1 hr. 5′
B. "Detoxified" Venom		
1:1000	0′ 13″	0′ 14″
1:2000	0′ 15″	0′ 29″
1:4000	0′ 23″	0′ 33″
1:8000	0′ 25″	1′ 10″
1:16000	0′ 40″	1′ 55″
1:32000	0′ 47″	9′ 50″
1:64000	3′ 15″	6′ 48″
1:128000	9′ 25″	40′ 0″
1:256000	1 hr. 45′	4 hrs.
1:512000	4 hrs.	18 hrs.

Clotting Effect of Venom on Fibrinogen. To determine the constituents of blood which might be acted upon by venom, the effect of venom on the conversion of fibrinogen to fibrin was studied. The addition of venom to a clear, dilute fibrinogen solution results in the formation of a cloudy gel-like fibrin clot, which undergoes lysis at a rate dependent on the concentration of venom. The usual Lee and White method for the determination of clotting time could not be used to measure this reaction because any agitation of this system resulted in the immediate retraction of the fibrin clot. Thus the end-point used in this technique, *i. e.*, the formation of a self-supporting clot, was seldom obtainable.

In order to obviate this difficulty a Summerson[10] photo-electric color-

imeter was used to follow the turbidity of the venom fibrinogen mixture during the clotting process and the following lysis, for after insertion of the colorimeter tube no agitation of the system is necessary. The rationale for the use of this instrument for the determination of the clotting time is as follows: The transformation of fibrinogen to fibrin is accompanied by an increase in the optical density of the system. The increased density is proportional to the amount of fibrin formed. Therefore the measurement of the resistance of this solution to the passage of light becomes a relative index of the amount of fibrin present. By this means the formation and lysis of the fibrin clot can be expressed in terms of the turbidity of the solution. Figure 1 illustrates the clotting and lytic action of "detoxified" venom on fibrinogen solution expressed in turbidity of the fibrin gel. The units of turbidity are arbitrary and represent the numbers on the colorimeter dial. The maximum reading (160) indicates the complete conversion of fibrinogen to fibrin. Time is recorded after mixture of all the constituents of the final solutions. Three experiments are represented: First (dot-dash line), a solution composed of 1 cc. fibrinogen solution, 4 cc. normal saline and 0.1 cc. (30 units) heparin was incubated at 32.5° C. for 1 hour. Then 0.25 cc. of 1% "detoxified" venom was mixed with the solution. Second (dotted line) 1 cc. fibrinogen was diluted with 4 cc. normal saline and to this mixture 0.25 cc. of 1% "detoxified" venom was added. Third (solid line), a solution composed of 0.25 cc. of 1% "detoxified" venom, 4 cc. normal saline and 0.1 cc. (30 units) heparin was incubated at 32.5° C. for 1 hour. Then 1 cc. fibrinogen was mixed with the solution. In each experiment, no change in the turbidity occurred for 13 to 20 seconds after the mixture of fibrinogen and venom. Then suddenly the turbidity increased rapidly so that within 40 to 60 seconds a very turbid, self-supporting gel was formed. Within the next 2 to 3 hours the gel underwent lysis resulting in a clear solution.

TABLE 2.—EFFECT OF THROMBIN AND "THROMBIN-LIKE" AGENTS ON FIBRINOGEN

	Fibrin* in mg. and in % of maximum yield (measured after 1 hour)					
	0.1 cc. thrombin		0.1 cc. (1–100) detox. venom		0.1 cc. (1–5000) stock venom	
Fibrinogen solution	Mg.	% max. yield	Mg.	% max. yield	Mg.	% max. yield
0.50 cc. fibrinogen + 0.50 cc. saline	680	100	590	87	610	90
0.25 cc. fibrinogen + 0.75 cc. saline	350	100	270	77	310	89
0.10 cc. fibrinogen + 0.90 cc. saline	137	100	97	71	97	71
0.05 cc. fibrinogen + 0.95 cc. saline	65	100	35†	54	35†	54

* Measured in terms of reconverted fibrinogen.
† Approximate readings.

Another method was used to corroborate the fibrinolytic action of the venom. In the determination of fibrinogen, according to the method of Bancroft, Stanley-Brown and Quick, 1 hour elapses between the mixture of the components and the recovery of the fibrin. It is apparent that when venom is used as the thrombic agent the fibrin formed is exposed to the lytic action of the venom for 1 hour. Thus the relative yield of fibrin after the action of venom on a known amount of fibrinogen is compared to the yield after action by thrombin which has no fibrinolytic power. The result may be expressed as the percentage of maximum yield. Table 2 shows this comparison. One cc. fibrinogen solution was mixed with 0.1 cc. of one of the thrombic agents; the mixture was allowed to stand 1 hour before the removal of the fibrin clot. The yield of fibrin in milligrams from thrombin and from venom is also given as a percentage comparison. The lytic action is thought to be responsible for the smaller yield from the action of venom.

B. *In Vivo Experiments.* Because of the marked clotting power of venom *in vitro*, an attempt was made to speed the clotting reaction in animals by its parenteral administration. *In vivo*, experiments were performed on white rabbits and small mongrel dogs. In some experiments the animal was in the fasting state, in others the time of the last meal was not controlled.

In rabbits, no alteration in the clotting time was observed and no local hemorrhage occurred after the subcutaneous injection of as much as 0.1 cc. of 1% "detoxified" venom. A slight and inconstant fall in the rabbit's clotting time (capillary tube method) was observed within an hour after the intramuscular injection of 1 to 2 cc. of "detoxified" venom. The determination of the clotting time by the capillary tube method was too inaccurate for measurement of small differences. After determining that intravenous doses of venom in rabbits caused an increase in coagulation time associated with a decrease in fibrinogen, it was decided to use dogs as the experimental animal and to determine the clotting time by the 8 mm. tube method using venous blood.

Seven dogs died 2 to 30 minutes after a single intravenous injection of 1 cc. or 2 cc. of 1% stock or "detoxified" venom. The animals exhibited gasping, vomiting, defecation, urination, opisthotonus, respiratory paralysis and cardiac asystole. Immediately before the injection of venom the clotting times of 2 dogs were 9 minutes, and 7 minutes, 45 seconds respectively, and their blood fibrinogen levels were normal. Blood obtained as early as 50 seconds after the injection of venom was permanently fluid and contained no fibrinogen. Large hematomata at the sites of the needle puncture occurred before death. All of the animals were autopsied shortly after death. The findings were remarkable for the absence of large or small blood clots in the chambers of the heart or in the great vessels. There was marked engorgement of the vessels of the viscera both grossly and microscopically. Stained sections of heart, lung, liver, kidney, spleen and small bowel showed no evidence of deposits of fibrin on the endothelium of the blood-vessels, on the red cells or in the capillaries. Dark-field examination of postmortem blood revealed no fibrin strands.

When only 0.1 cc. of 1% "detoxified" venom diluted to 10 cc. with normal saline was injected rapidly intravenously into each of 4 dogs, the animals survived and showed only mild toxic signs. There was no positive phase (shortening) of coagulation. In 3 dogs clotting times determined 13 minutes, 23 minutes, and 30 minutes, respectively, after injection, were indefinitely prolonged and remained prolonged for 8 to 24 hours. Blood drawn from the fourth dog 38 minutes after the injection formed a friable, non-supporting clot in 40 minutes which was lysed in 4 hours. In each dog the prothrombin levels fell from 100% to 50 or 60% of normal and remained low for as long as 48 hours. No fibrinogen was demonstrable in the blood drawn as long as 4 hours after venom injection, but it returned to the normal range in 24 hours. A single additional experiment on the effect of an intramuscular injection of 0.25 cc. of 1% "detoxified" venom in a dog was performed. The clotting time, prothrombin and fibrinogen values did not change significantly over a period of 1 hour and 25 minutes.

C. *Antivenom Experiments.* As can be seen from the above experiments, the venom was found to have a marked coagulating effect *in vitro* and a marked anticoagulating action *in vivo*. Therefore it was considered possible that two factors were involved. It was thought that an antivenom could be developed which might neutralize the anticoagulating factor and thus only the coagulating effect would be manifested *in vivo*. In an attempt to develop this antivenom, each of 3 rabbits was injected subcutaneously every 3d day for 2 months with a gradually increasing dose of venom. The total amount each rabbit received varied from 5.9 to 6.6 cc. of 1% "detoxified" venom. At the end of 2 months, blood serum was obtained from the

rabbits and was pooled. *In vitro*, 0.2 cc. of varying strengths of "detoxified" venom were mixed with an equal quantity of graded serum dilutions and incubated for 1 hour at 37° C., then kept in an ice-box for 12 hours. Marked flocculation occurred in a mixture of equal quantities of a 0.05% "detoxified" venom solution and undiluted rabbit antivenom serum. The greatest flocculation occurred when a dilute venom solution was mixed with undiluted serum. In such proportions the rabbit antivenom serum was able to nullify completely the clotting action of venom. For example, an amount of venom which clotted oxalated blood in 15 seconds was rendered impotent by the addition of antivenom serum.

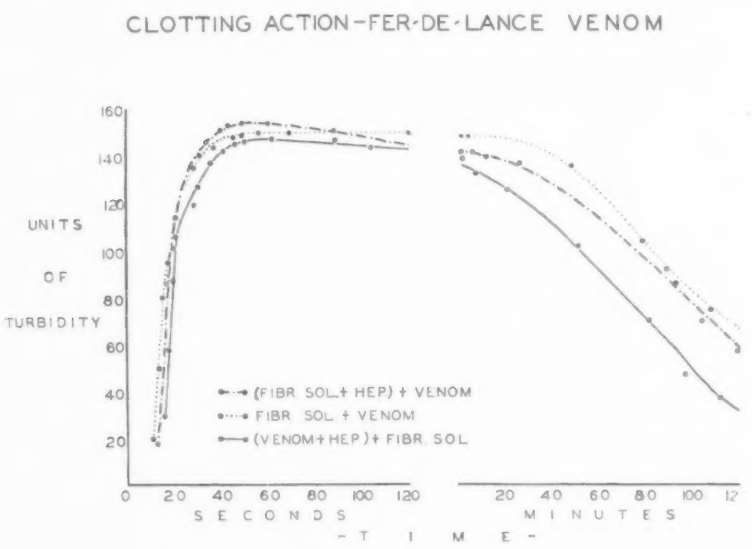
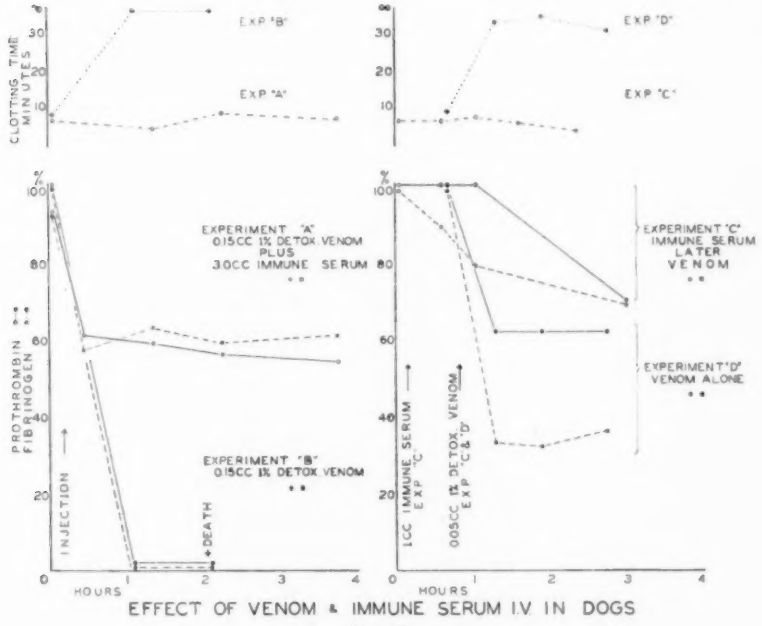


FIG. 1.

Several experiments on dogs were then performed to test the *in vivo* effect of the rabbit antivenom serum. Figure 2 illustrates the results of 4 intravenous experiments performed on 2 dogs. In Experiment A a dog was given an injection consisting of 0.15 cc. of 1% "detoxified" venom, 3 cc. rabbit antivenom serum and 2.85 cc. normal saline. This proportion of venom to antivenom serum was equivalent to that giving the greatest flocculation *in vitro*. Following the injection, the clotting time remained within the normal range while the prothrombin and fibrinogen fell to approximately 60%. In Experiment B the same dog received the same amount of venom without antivenom serum. The clotting time became indefinitely prolonged while the prothrombin and fibrinogen fell to zero. The dog died about 2 hours after the injection, having exhibited signs that accompany a lethal dose of venom. In Experiment C the proportion of venom to antivenom serum was the same as in Experiment A but the quantities were smaller. The serum was injected 40 minutes before the injection of venom. The results were comparable to those of Experiment A. Finally, Experiment D is a typical illustration of an intravenous injection of a sublethal amount of venom into a dog not protected by antivenom serum.

Two additional experiments on dogs were carried out to determine whether normal rabbit serum possessed any protective action against

"detoxified" venom. The first animal was given intravenously a solution of 0.1 cc. of 1% "detoxified" venom, 2 cc. normal rabbit serum and 1.9 cc. physiologic saline. Contrary to what might be expected, in a period of 1 hour and 30 minutes following this injection, the clotting time showed no significant change; the prothrombin fell from 100% to 64%; the fibrinogen fell to 33% of its initial value. The second dog was given intravenously a solution of 0.15 cc. "detoxified" venom, 1.9 cc. normal rabbit serum and 4 cc. physiologic saline. One hour and 2 hours following the injection the clotting times were greatly prolonged; the prothrombin was 58% and no fibrinogen could be demonstrated in the blood. Pertinent to these results are those obtained *in vitro* when 0.25 cc. of rabbit antivenom serum or 0.25 cc. of normal rabbit serum was mixed with either 1 cc. of oxalated blood or 1 cc. of fibrinogen solution. Twenty-four hours after mixture soft, friable clots were present in all tubes. The normal serum had the same degree of thrombic action as the antivenom serum.



EFFECT OF VENOM & IMMUNE SERUM I.V. IN DOGS

FIG. 2.

D. *Postinjection Plasma ("Plasma de Venins") Experiments.* The remaining experiments to be reported concern the clotting property of the plasma of dog's blood drawn after an intravenous injection of snake venom. One of the properties of the plasma obtained from blood which has been rendered incoagulable by venom is its ability to clot oxalated whole blood. The mechanism involved in this reaction has remained obscure although much work has been done on this problem.[5,6] It seemed that the development of the antivenom serum described in the above experiments allowed this problem to be attacked from a new angle, since any thrombic activity of the venom could be nullified by the addition of antivenom serum. Experiments were devised to test the effect of antivenom serum on the post-injection plasma. Blood drawn both before and after the intravenous injection of "detoxified" venom was oxalated and centrifuged. The cell

free supernate was removed. This supernate will be referred to as plasma. It was repeatedly observed that the addition of postinjection plasma to normal oxalated blood resulted in the prompt clotting of the blood. No clotting occurred after the addition of pre-injection plasma or of physiologic saline. This clotting property of the postinjection plasma was always apparent if the amount of venom injected was sufficient to have caused the dog's blood to become incoagulable. A dog was given 0.08 cc. of 1% "detoxified" venom intravenously. Thirty minutes later the clotting time was indefinitely prolonged, the prothrombin 30% and the fibrinogen zero. Two 18 cc. specimens of blood were drawn and oxalated, one specimen before the injection of venom, the other 30 minutes afterwards. To one-third of each of these specimens 1 cc. normal saline was added; to the second third, 1 cc. of normal rabbit serum; and to the remaining third, 1 cc. of rabbit antivenom serum. The plasmas were then removed from each of the various subspecimens and their clotting properties tested by adding 0.5 cc. of each plasma to 1 cc. normal oxalated blood and 1 cc. fibrinogen solution, respectively. Observations were made for 4 hours. No clots were observed in any of the mixtures containing pre-injection plasma or a combination of postinjection plasma and antivenom serum. Prompt clotting occurred in the mixtures containing postinjection plasma not combined with antivenom serum. The antivenom serum had thus nullified the clotting power of the postinjection plasma. Calculation of the final amount of venom in the oxalated blood and fibrinogen solution revealed that there was about 1 part in 125,000, which according to Section B of Table 1 clotted oxalated whole blood in about 9 minutes and 25 seconds. Since clotting occurred in these "plasma de venins" studies in 35 minutes it is probable that the entire thrombic activity of the postinjection plasma is due to the venom it contains as undoubtedly some of the venom is utilized in the clotting reaction.

Discussion. *In vitro*, *B. atrox* venom is an effective clotting agent in dilutions of 1:500,000. The venom acts as a thrombin as is shown by its ability to convert fibrinogen to fibrin, and also as a fibrinolysin when it is present in relative excess. Heparinized blood is clotted less rapidly than is oxalated blood. Jorpes[8] believes that heparin is an anti-thrombin; but in the foregoing experiments, heparin did not influence the thrombic action of venom on the second phase of coagulation.

Hanut[4] reports a positive phase of coagulation (shortening of the clotting time) after the parenteral injection of fer-de-lance venom in rabbits. Considering the errors inherent in the capillary tube method for determining clotting time, the slight reduction in the clotting time observed in rabbits following injection of large amounts of venom is not regarded as significant. Using the 8 mm. tube method for determining the clotting time, dogs show no positive phase of coagulation. Determinations were made as early as 50 seconds after the injection of venom. Intravenous injection of venom causes a fall in prothrombin and fibrinogen blood levels, but fibrinogen is the more readily affected. Both are reduced to zero when the amount of venom injected is lethal.

One of the most baffling problems raised by the experiments here reported is the striking difference between the clotting effect of fer-de-lance venom on whole blood *in vitro* and *in vivo*. The

addition of 0.002 mg. of "detoxified" venom to 1 cc. of oxalated whole blood results in solid clot formation in 1 hour and 45 minutes. When the same amount of venom per cc. of blood is injected intravenously into a dog the blood becomes indefinitely incoagulable and the animal dies in 25 minutes. Absolutely, this is of course a much larger amount of venom, which conceivably might be harmful through a selective fibrinolytic effect. There is no demonstrable prothrombin or fibrinogen in the blood drawn immediately before death. One-tenth of this amount of venom has no clotting effect on blood *in vitro*, but *in vivo* causes the blood to become incoagulable with marked depression of prothrombin and fibrinogen. There is a slow return of the animal's clotting power in 8 to 26 hours. Some workers[7,9] have suggested that the explanation of this difference in effect might be found in the mechanical difference in precipitation of fibrin *in vitro* and *in vivo*. Regarding the fibrinogen-fibrin conversion, 3 possibilities, which would explain the incoagulable blood *in vivo*, come to mind. The circulating fibrinogen might be precipitated as intravascular fibrin plugs. Macroscopic and microscopic examination revealed no plugging of the vessels. The fibrin formed might be dispersed as finely divided particles. Dark-field examination of the incoagulable blood revealed no such particles. The fibrin formed by the venom injection might be rapidly lysed. Concerning this hypothesis, it can be shown that the amount of venom present in the circulating blood before death is of the order of 1 part in 1,000,000. Since appreciable fibrinolysis *in vitro* occurs only when the venom is present as 1 part in 1000, it is difficult to assume that the fibrin is removed from the blood by lysis. All that can be said then is that *in vitro*, fer-de-lance venom has a coagulating and an anticoagulating (fibrinolytic) action on whole blood, whereas *in vivo* (using dogs as the experimental animal) only the anticoagulating effect is evident.

The development of an antivenom serum in rabbits is described. This serum nullifies the clotting action of venom in the test tube and protects dogs from an otherwise lethal intravenous injection of venom. *In vivo*, normal rabbit serum would seem to possess a less marked protective action as shown by the fact that the clotting time may remain within the normal range while the prothrombin and fibrinogen values are depressed. *In vitro*, rabbit serum apparently possesses a weak thrombic action. This is interesting in relation to the recent work on a thrombin-like factor obtained from rabbit plasma.[2]

There is no evidence that dogs become sensitized to repeated parenteral administration of venom. It was observed that an animal showed progressively fewer toxic signs when injected repeatedly with a given amount of venom. Rabbits tolerate a far larger dose of venom than do dogs.

The clotting action of postinjection plasma is apparently due to the contained venom. The speed of clot formation caused by this

plasma is of the same order as that exhibited by venom in a like dilution. The clotting power of this plasma is nullified by rabbit antivenom serum.

Summary. 1. *Bothrops atrox* venom is a powerful coagulant of whole blood and fibrinogen solution *in vitro*, but when administered to dogs intravenously it produced marked prolongation of the clotting time with a reduction in prothrombin and fibrinogen.

2. An antivenom serum was developed in rabbits which completely neutralized the clotting properties of the venom *in vitro*.

3. *In vivo*, this antivenom serum modified the effect of the venom on the clotting time, blood prothrombin and fibrinogen, and also protected dogs from a lethal dose of venom.

4. Normal rabbit serum had a slight protective action against the toxic effects of intravenous administration of fer-de-lance venom.

5. The thrombic activity of postinjection plasma or "plasma de venins" was due to the venom present.

6. The difference in action of fer-de-lance venom *in vitro* and *in vivo* was not clarified by these experiments.

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A CRITICAL STUDY OF THE ACTION OF 3–3′–METHLYLENEBIS (4–HYDROXYCOUMARIN) (DICOUMARIN)*

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The synthetic compound "dicoumarin" (3–3′–methylenebis [4–hydroxycoumarin])† isolated and synthesized by Link and his

* The expenses of this investigation were defrayed in part by a grant given "In recognition of Dr. Francis W. Peabody's Services to the Foundation" by the Ella Sachs Plotz Foundation.

† We are indebted to Dr. K. P. Link, of the University of Wisconsin and the Abbott Laboratories, North Chicago, Ill., for the dicoumarin used.

co-workers[3] has been suggested as a substitute for heparin in clinical therapeutics by several investigators.[1,2,15] We report here an investigation of a small group of patients treated with this substance. The investigation was undertaken to evaluate the drug critically, to compare its action with that of heparin, and to determine the precautions that should be employed when the drug is used. Our results confirm those of other investigators[1,2,15] that the drug when administered orally prolongs the prothrombin clotting time, and to a less extent the whole blood clotting time.

Methods. Patients receiving the drug were in all instances studied daily. Coagulation time of venous blood at 37° C. was measured by a modification[8] of the Lee and White method.[7] Prothrombin time was determined by a modification[9] of Quick's method.[10] In all cases determination of the coagulation time was made both in glass and in lusteroid tubes. The technique for the determination of coagulation time in lusteroid is as follows: Blood was drawn with stasis from an arm vein into a syringe lined with mineral oil. The needle was removed and 2 ml. of blood were placed in each of two lusteroid tubes 100 x 13 mm. in size. The tubes were examined in the same way as the glass tubes. The normal coagulation time in lusteroid tubes using the above technique is from about 25 to 50 minutes at 37° C. It is to be emphasized that the use of a lusteroid tube not only prolongs the coagulation time above that measured in glass, but also serves to magnify small variations in it. In a like manner any errors of technique such as a poor venepuncture with admixture of tissue juice, or a tube not scrupulously clean, lead to gross changes in the coagulation time. Even though these errors were kept at a minimum, variations occurred which rendered it only a relatively crude method. Nevertheless, the use of the lusteroid technique proved to be of considerable value.

The usual procedures for intravenous bromsulphalein, hippuric acid excretion (oral), and urine urobilinogen excretion (roughly quantitative) were used in a number of patients as liver function tests, through the courtesy of Dr. Emmanuel Deutsch of the Surgical Research Laboratories of the Boston City Hospital.

Experimental. 1. *Effect on Prothrombin Concentration.* Eight individuals from 12 to 69 years old were studied. Two of them were convalescent from mild illnesses and may be regarded as normal. Of the remaining 6 subjects, 4 had thrombophlebitis, 1 had endocarditis lenta, and 1 survived suture of a puncture wound of the heart. Chart 1 shows an example of a case given dicoumarin with changes in prothrombin concentration and coagulation time measured in glass and lusteroid tubes.

The first action of dicoumarin was always displayed as a fall in the prothombin concentration. Taking a fall to 30% of the normal prothrombin concentration as a criterion of definite effect of the drug, 3 of our patients responded within 24 hours whereas the remainder required from between 48 hours and 5 days to give such a response. One cannot predict when a response will occur in any individual following a given dose of the drug. A number of factors appear to modify the time of onset of the action: the size of the initial dose and of subsequent doses in relation to body weight; the initial level

of prothrombin concentration in the blood; an apparently large and unpredictable variation in individual response to the drug.

The effect of the substance, once low prothrombin concentrations are reached, is quite prolonged. Chart 2 shows the effect of a single large dose (15 mg./kilo) of the drug upon the prothrombin concentration of an apparently normal individual. A prothrombin concentration of below 30% of normal was maintained for 5 days and the concentration was not within normal limits for 5 more days. Most of the patients received an initial dose of from 3 to 12 mg./kilo and thereafter a daily dose of from 0.1 to 0.2 gm. Using this dosage the prothrombin concentration was maintained at very low levels and, with one exception, from 5 to 11 days were required after the drug was stopped before the concentration of prothrombin rose above 50%. When this level was reached the return to normal was always prompt.

The prothrombin time with the thromboplastin used has a normal value of from 25 to 30 seconds. The amount of prolongation of the Quick prothrombin time is of interest when interpreted as prothrombin concentration and especially when this concentration is compared with the plasma recalcification time and coagulation time of whole blood. In calculating prothrombin concentrations a curve was used which was obtained by plotting the prothrombin time of a series of appropriately modified plasmas. To accomplish this the prothrombin time was determined from varying concentrations of normal plasma, mixed with the same plasma passed through a Seitz filter 5 times. It has been shown that when plasma is passed through a Seitz filter 5 times, it becomes incoagulable with thromboplastin and calcium for more than 2 hours at least.[6] Using this curve a prothrombin time of about 60 seconds corresponded to approximately 10%, 90 seconds to 5%, and 150 seconds to 2.5%, of the normal plasma prothrombin concentrations respectively. A prothrombin time of greater than 150 seconds was simply called less than 2.5% of normal. In many of the patients given dicoumarin the Quick prothrombin time was extraordinarily prolonged. One patient after receiving a total of 31 mg. of dicoumarin per kilogram body weight during a period of over 8 days had a prothrombin time of greater than 1 hour (Chart 1). The drug was discontinued and the next day the prothrombin time was 40 minutes and in the subsequent 6 days gradually fell from 17 minutes to 3¼ minutes or about 2.5% of the normal concentration of prothrombin. These extraordinarily prolonged prothrombin times are of interest in themselves for they certainly suggest the great reserve of prothrombin in plasma above that required for coagulation. Moreover, when these figures are compared with the whole blood coagulation time on the same day one finds that when the prothrombin times were on one occasion over 1 hour and on another 40 minutes, not only did the whole blood still clot, but it did so in the relatively

short time of 17½ and 19 minutes respectively. These whole blood coagulation times were indeed much shorter than the prothrombin time itself. The recalcification time of citrated plasma in these instances was 9 minutes and 10 minutes respectively, both normal values for the procedure and again far shorter than the prothrombin time. Thus, curiously enough, the recalcification time after the addition of an excess of thromboplastin (prothrombin time) was far longer than the recalcification time without the addition of this substance. This phenomenon was observed on several occasions and requires further study.

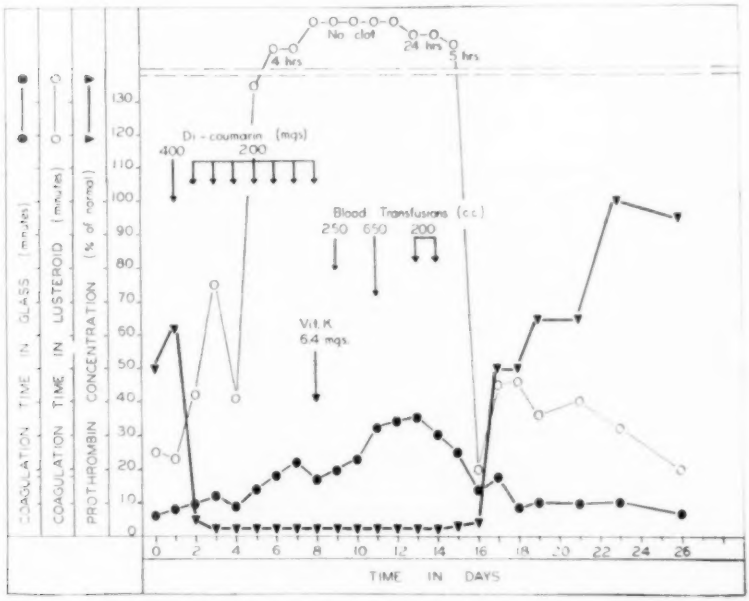

CHART 1.—Changes in the coagulation time in glass and lusteroid and the prothrombin concentration following the administration of 1.8 gm. of dicoumarin. Effect of the administration of vitamin K and whole blood transfusions.

2. *Effect on the Coagulation Time.* The effect of the administration of dicoumarin upon the coagulation time of blood measured in glass and lusteroid tubes was extremely variable. In general the coagulation time became prolonged as the prothrombin concentration reached low levels. However, there was no parallelism of the two in any one patient, and further, some of the patients had a moderately prolonged coagulation time without profound lowering of the prothrombin concentration. In general, however, the coagulation time was not significantly prolonged until the prothrombin concentration reached very low levels, usually less than 5% of normal. The coagulation time measured in lusteroid tubes showed

a much greater prolongation with reduction in prothrombin concentration, than that in glass tubes. Furthermore, the rise in clotting time in lusteroid tubes was sometimes, but not always, 24 hours earlier than the change detected in clotting time in glass. The coagulation time in lusteroid was often not measurable when the prothrombin concentration was very low due to the end-point being spread over many hours. Occasionally the blood in lusteroid tubes failed to clot under 24 hours.

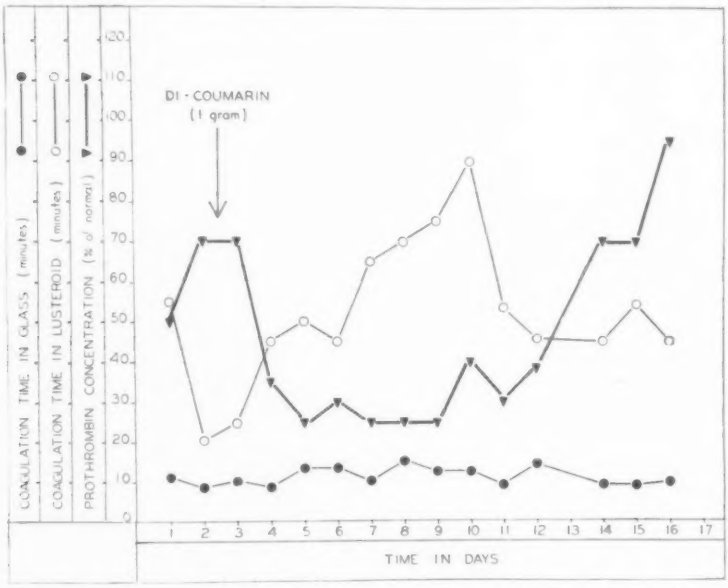

CHART 2.—Changes in the coagulation time in glass and lusteroid and the prothrombin concentration following the administration of a single oral dose of 1 gm. of dicoumarin, in a normal human.

Lozner and Taylor[8] have shown that the effect of surfaces such as lusteroid in prolonging the coagulation time is not upon the blood platelets, but upon some property of platelet free plasma, possibly upon the "globulin substance" known to be active on but deficient in hemophilic blood. One might suppose, then, in view of the long, often very long, coagulation time in lusteroid tubes, that the plasma of patients receiving dicoumarin may have been deficient in this "globulin substance." However, we have consistently been able to hasten the coagulation of hemophilic blood, *in vitro*, as much by the addition of 0.1 ml. of plasma from patients receiving dicoumarin to 2 ml. of hemophilic blood, as by the addition of equivalent amounts of normal plasma. Thus there seems to be no modification of the action of the "globulin substance" by dicoumarin. One may suggest therefore, that whatever the rôle of the "globulin substance"

in blood coagulation may be, in plasma from patients receiving dicoumarin its lessened effectiveness probably is due to a diminished prothrombin, rather than to any change in "globulin substance" itself.

The proteolytic enzyme from plasma and serum produced by the action of chloroform, reported by Tagnon and his associates[12,13] and said to be deficient in hemophilia,[14] was found to have normal activity even when the prothrombin concentration of the plasma was only 2% to 5% of normal. From such comparative studies it would appear that dicoumarin had no effect either upon the essential activity of "globulin substance," which Howell[5] calls "plasma thromboplastin," nor upon the proteolytic enzyme.

In most of the patients studied, the following data were obtained every 2 to 3 days: hemoglobin concentration, red cell count, hematocrit and red cell volume studies, differential and total white cell count, icteric index and platelet count. In one patient a moderate normocytic normochromic anemia developed. No such change was found in any of our other subjects. No changes in the differential or total white cell count were found, except those compatible with the changing clinical state of the patient's infection when present. Bleeding time (Duke method) was performed repeatedly on several of the patients but no prolongation was found. For example, one patient after dicoumarin administration, when the prothrombin time was greater than 1 hour and the coagulation time in glass 17½ minutes, had a bleeding time of 1 minute.

3. *Effect on Plasma Protein and Liver Function. Determination of plasma proteins:* albumin, globulin and fibrinogen (as fibrin) were made on several patients. There were no significant changes.

Because of its chemical constitution and because prothrombin is generally accepted as being manufactured in the liver, hepatic function tests were done on the individuals receiving dicoumarin. No significant change was found.

4. *Effect of Vitamin K and Blood Transfusion.* Our results agree with those of others[1,2,15] that no effect on prothrombin concentration is produced when adequate doses of synthetic vitamin K were administered intramuscularly to patients receiving dicoumarin with a prothrombin concentration of less than 2.5% of normal.*

Transfusions have been reported as having a variable effect upon the coagulation time and prothrombin concentration of patients receiving dicoumarin.[1,2,15] One of the patients under investigation received 0.9 gm. of dicoumarin and his prothrombin fell to approximately 2.5% of normal. A transfusion of 500 ml. of whole blood was administered and, as may be seen from the curve (Chart 3), a rise to 10% of the normal prothrombin concentration was obtained

* We have given 60 mg. of synthetic vitamin K parenterally to a patient receiving dicoumarin without any change in the greatly reduced prothrombin concentration.

which gradually fell again, but never to its original low level. The prothrombin concentration of the blood administered was normal. In contrast to this, another patient (Chart 1) was given repeated transfusions of whole blood without any striking effect upon the very low prothrombin concentration or prolonged coagulation time.

Discussion. It is impossible to make an adequate estimate of the clinical effectiveness of dicoumarin from a few cases and this was not the purpose of this report. However, whether associated with the drug therapy or not, clinical improvement in the cases of thrombophlebitis was uniform with the exception of 1 patient, who died of sepsis.

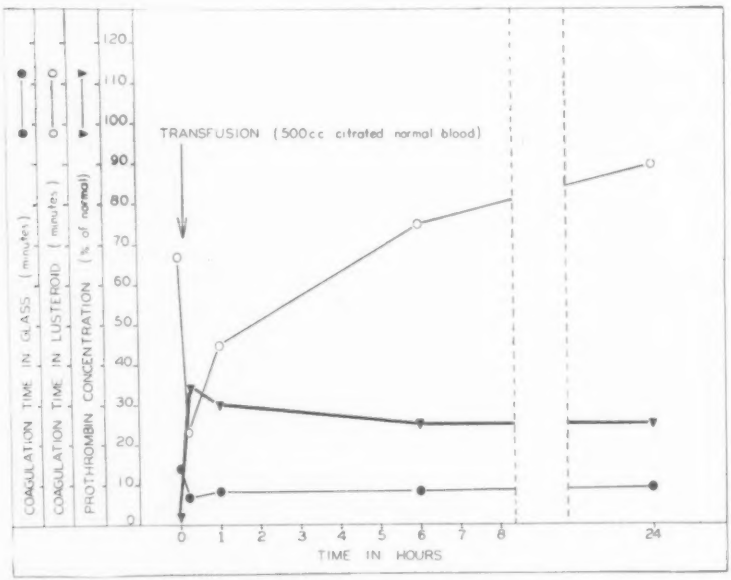

CHART 3.—Effect of a whole blood transfusion on the changes in coagulation time in glass and lusteroid and prothrombin concentration produced by the administration of dicoumarin.

No serious bleeding episodes occurred, except in the case of endocarditis lenta who had an increase in bleeding and purpuric manifestations following administration of the drug. This poor result in endocarditis lenta should be emphasized, for one is tempted to use anticoagulant therapy in this disease and other septic thromboses.

The clinical use of heparin in thrombophlebitis, phlebothrombosis, and vascular surgery has come into vogue in recent years, but its use has been hindered by the expense of the drug and by its transient effect, necessitating frequent administration or continuous intra-

venous drip. The administration of one dose of heparin will prolong the coagulation time of blood to from 30 to 60 minutes without any difficulty, and such a change may be maintained for hours or days. Following the discontinuance of heparin the coagulation time of the blood returns to normal within a few hours; the time depending upon the dose administered. For example if 5500 Connought units are given in one dose one may expect the coagulation time to be normal within 3 hours. Furthermore, if protamine (*e. g.* salamine sulphate) be administered in calculated amount, to a patient receiving heparin, the coagulation time returns to and remains normal within 5 minutes (Chart 4). Protamine has no such antagonistic effect to dicoumarin and to the present no other antidote, other than blood transfusion, is available for use in an unexpected emergency.

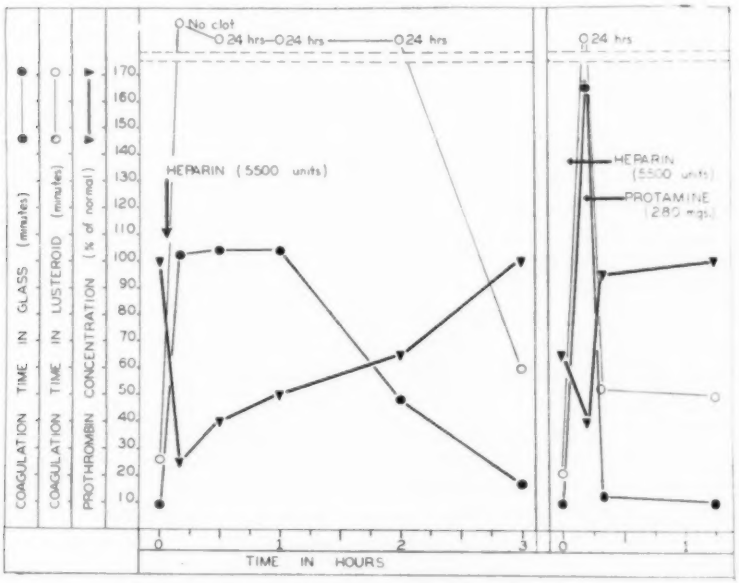

CHART 4.—Effect of administration of heparin and of heparin followed by protamine (salamine sulphate) upon the coagulation time in glass and lusteroid and prothrombin concentration in a normal human.

Dicoumarin has been proposed as a less expensive orally active substitute for heparin. It is clear that the chemical nature and mode of action of the two drugs is quite different. Heparin acts as an anticoagulant both *in vitro* and *in vivo*, whereas dicoumarin has its effect only *in vivo* and delays blood coagulation by its action upon prothrombin. Very low prothrombin concentrations must be attained before clotting is significantly delayed. Furthermore, the effect on coagulability is not constant, nor is it in any case nearly as

marked as the change after heparin administration. In the cases we have studied, enough dicoumarin compound to prolong the coagulation time significantly has an action which continues for many days after the drug is discontinued (Chart 1) and, further, this effect is not mitigated by the administration of vitamin K or transfusion of whole blood unless the drug effect is small or wearing off in which a transient effect may be noted from blood transfusion. The ineffectiveness of vitamin K on the coagulation and prothrombin time of blood of patients under dicoumarin therapy has been previously reported,[1,2,15] as has the variable effect of blood transfusions.[1,2,15] It has been suggested that the administration of dicoumarin compound be controlled so that the prothrombin concentration be kept within "reasonable limits."[15] However, to obtain a fairly constant and significantly delayed coagulability of the blood one must reduce the prothrombin concentration to very low levels, and if this is done the effect of the drug cannot be adequately controlled. Thus one must sacrifice control for effectiveness or *vice versa* and therefore caution must be used when the administration of dicoumarin is proposed as a heparin substitute.

Summary. 1. The effect of the synthetic compound 3-3′-methylenebis (4-hydroxycoumarin)—dicoumarin—upon the coagulation of blood and upon certain blood constituents was studied in detail in a small group of patients.

2. The drug was found to act by diminishing the effective prothrombin concentration in the blood, sometimes to very small amounts.

3. The prolonged blood coagulation time observed is apparently secondary to the low prothrombin concentration, but was not constant nor was it of marked degree unless large doses of the drug are administered.

4. The coagulation time measured in "Lusteroid," although more variable than in glass, showed much greater delay in clotting than in glass after the administration of the drug. The suggestion was made that the coagulation time in "Lusteroid" indicates the true coagulation defect more closely than does glass.

5. The occurrence of prothrombin clotting times longer than recalcified plasma clotting time was observed and the possible significance of the finding discussed.

6. The relation of the abnormal clotting mechanism to other coagulation factors: foreign surface, platelets, "globulin substance," and plasma proteolytic enzyme was studied and the results discussed.

7. The effect of the administration of the drug upon blood cytology, liver function, plasma proteins, especially fibrinogen, was studied and no significant abnormalities found.

8. Vitamin K (synthetic) was found not to act in any way as an antidote to the effect of administration of the drug.

9. Whole blood transfusion was found to have only a transitory effect or no effect upon the abnormal clotting mechanism in patients receiving the drug.

10. It is suggested that the variable effect of the drug upon blood coagulability, its prolonged action after discontinuation, and its difficulty in control render the drug a poor heparin substitute, and that great caution must be used in its administration.

The authors wish to express their appreciation to Dr. George R. Minot and Dr. F. H. L. Taylor for their advice and help, and to Miss Margaret Adams for protein determinations.

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SIX AUTOPSIED CASES OF DISSEMINATED LUPUS ERYTHEMATOSUS

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Disseminated lupus erythematosus nearly always leads to the death of the relatively young women who are its usual victims. The etiology is unknown. In the hope of adding to the understanding of the disease, 6 cases observed clinically and at autopsy at the New York Hospital are here described.

Reports of this condition already in the literature are not enumerated because of ill-defined diagnostic criteria. Some cases in the erythema group described by Osler[5] in 1895 and 2 of the cases

described by Libman and Sacks[3] in 1923 might now be listed as disseminated lupus erythematosus. Autopsied cases: Baer described 23 in 1935; Rose and Pillsbury[7] reported 5 cases in 1939. The Reifensteins[6] added 1 case of their own in 1939, studied selected, reported cases, and gave an excellent review of the literature on the disease. There are many other reports[2,4] of small numbers of cases.

Definite diagnostic criteria for this condition need to be established. The following definition has been suggested:[6] "A diffuse peripheral vascular disease associated with lupus erythematosus and glomerulonephritis." The disease occurs in women of the childbearing age; one probable case, however, has been autopsied in a 25-year old man and other cases have been suspected in men. Joint pains are frequent. The course is marked by exacerbations and remissions with fever, weight loss, and episodes of pericarditis and pleurisy. A terminal bronchopneumonia is the rule. The "butterfly" skin lesion is present for a long or a short time. The blood shows a secondary anemia and a leukopenia. The urine often shows small or moderate amounts of albumin with red cells and casts. Renal function may be impaired. According to present methods, blood cultures are negative. The Mantoux test may or may not be positive but evidence of active tuberculosis in connection with the disease is lacking. At autopsy involvement of the pleural and pericardial surfaces is usually found. Renal lesions are present in some cases. There may or may not be verrucous endocarditis. There is often widespread involvement of the small bloodvessels, marked by intimal proliferation and fibrosis, with degenerative changes in places in the walls, narrowing of the lumina and occasional thrombus formation.

The 6 cases here reported were observed by members of the resident and attending staff at the New York Hospital from 1936 to 1940. The histologic material has been reviewed for this report by Dr. William Dock; he has contributed the tabulations regarding the pathologic findings. The rest of the data has been taken from the hospital records.

Case 1.—E. W., a 36-year-old, married, Swedish woman was first seen in the Out-patient Department in August 1936 complaining of a facial eruption present for 9 years. A scrofulous neck gland was removed at 10 years and pleurisy was diagnosed at 28 years. At 27 years small, red, scaly, itchy areas appeared below the eyes, spread laterally to assume a butterfly shape and disappeared after about 6 weeks. A similar eruption appeared each spring for the next 4 years, then persisted. A series of gold sodium thiosulphate and bismuth salicylate injections were given in the Out-patient Department of the New York Hospital in August and September, 1936.

In October 1936 the patient was admitted to the hospital with a temperature of 39.4° C. She was fairly well-nourished. Over the nose and entire face was a butterfly lesion, indurated and red, with elevated edges, showing marked scaling in places. The axillary nodes were enlarged. Urinalysis was normal. The hemoglobin was 94% (13.7 gm.) with 4.4 million red

blood cells. The white blood cell count was 5000 with 20% immature neutrophils. The blood Kline test was negative.

The skin lesions cleared promptly; the temperature returned to normal; treatment with bismuth and with gold sodium thiosulfate was resumed. In May 1937 the left ear began to drain. A few months later joint pains set in. Vaccine prepared from the ear discharge, and later bee venom injections, were given without improvement in the joint symptoms. The skin lesions recurred. During the following months progressive weakness and weight loss occurred with fever to 39° or 40° C. much of the time.

In August 1938 a sharp pain in the right chest with cough set in. The patient was readmitted to the hospital. She appeared cachectic. Over the entire body were numerous fiery red, scaly, dried papular lesions. There were superficial ulcerations on the buccal mucosa. There was a purulent discharge from the left ear. There were scattered râles at the lung bases. The blood pressure was 110/68. There was widespread involvement of the joints with pain and limitation of motion. After 9 days in the hospital, signs of the left lower lobe consolidation appeared; weakness and respiratory distress increased until the patient died a week later. Blood cultures were negative.

Histologically the spleen and lymph nodes showed hyperplasia, without activation, or "germinal centers"; chronic pericarditis was present; the mitral valve showed no changes nor were changes present in the kidneys save agonal degeneration of the tubules and hyperemia. There was hyaline intimal thickening of the splenic arterioles.

Anatomic Diagnosis. Chronic dermatitis with disseminated cutaneous scars; bronchopneumonia (left lower lobe); bronchitis with bronchiectasis; purulent pleurisy of the interlobar septum; bilateral serous pleural effusion; chronic pericarditis with fibrous adhesions; a focal vascular scar of one kidney; calcified tuberculous nodules in the mesenteric nodes; acute inflammation of the tracheal and tracheo-bronchial nodes; moderate hyperplasia of the superficial mediastinal, para-aortic, and iliac nodes; serous peritoneal effusion; focal fatty degeneration of the liver; petechiæ in the gastric mucosa, os uteri, and urethra; chronic arthritis with focal atrophy of cartilage of the right knee joint, with thickening of the synovial membrane and serous effusion in the joint.

Case 2.—B. H., a 28-year-old single American woman, was admitted to the New York Hospital in December 1936 complaining of painful swollen joints for 11 months. In April 1936 a sunburn was followed by a severe skin rash diagnosed lupus erythematosus in another hospital where retinitis was observed. Anemia was also found and transfusions were given.

Physical examination showed a thin, pale woman with a large ulcer on the soft palate. The spleen was just palpable. The blood pressure was 120/70. Urine, sp. gr. 1.025, albumin, 2+ and occasion granular casts. Hemoglobin, 10.2 gm., 3.9 million red cells. The white blood cells ranged from 5000 to 10,000 per c. mm. (15 to 32% immature neutrophils and 2 to 3% eosinophils). The blood Kline test was negative; blood urea nitrogen, normal. Blood cultures were negative.

Several blood transfusions were given. Skin lesions typical of lupus erythematosus developed during the first month of observation and new mouth ulcers appeared. In January 1937 severe convulsions and signs of spasticity in the extremities occurred and cystitis developed. In March, pus appeared in the bursa over the right knee and later an abscess developed about the right hip. Hemolytic streptococci were found in these sites. A course of Prontylin was given without appreciable effect. The Mantoux test was positive to 0.01 mg. of O. T. The patient became increasingly weak and thin and died in November 1937 after several days in a delirious state with signs of terminal bronchopneumonia and pleural effusion.

Histologic examination showed much hemosiderin in the spleen; disseminated tuberculosis in the lymph nodes; no changes in the mitral valve; focal interstitial nephritis resulting from pyelonephritis and some swollen glomerular tufts. No "wire loops" or hyaline thrombi were seen in the kidneys nor was distinct periarteritis found. The splenic arteries were unchanged but there was lymphocytic infiltration about the endothelium of the trabecular veins.

Anatomic Diagnosis. Disseminated lupus erythematosus with hemorrhages in the subcutaneous tissues underlying erythematous patches; bronchopneumonia of both lower lobes with pleural effusion bilaterally, serofibrinous in type; serofibrinous pericarditis; bilateral chronic pyelonephritis with focal atrophy of the renal cortex; right urethritis, and hemorrhagic cystitis; tuberculosis of the periportal and periaortic nodes, with caseation; general lymphoid hyperplasia; a small fibrotic tubercle of the spleen; peripheral fatty degeneration of the liver; hemorrhages in the duodenal submucosa; chronic arthritis, with serofibrinous effusion in each knee joint with focal atrophy of cartilage. Ulcers were present over the sacrum, hips, and knees.

Case 3.—G. H., a 30-year-old woman of Polish descent, was admitted to the hospital in April 1937 complaining of pain in her right chest and right upper abdomen for 3 weeks. Bilateral purulent otitis media at 22 years led to deafness. The following year joint pains in the hands began; these recurred at 24 years following an abortion and at 26 years following a normal delivery. At 29 years there occurred epistaxes, a low grade fever, petechiæ, and a butterfly facial eruption for a period of several weeks.

Physical examination showed an emaciated woman who appeared chronically ill. There was a large anterior perforation of the nasal septum. Breath sounds were diminished at the lung bases and râles were present. The finger joints were stiff. Extension of the right elbow was limited. The blood pressure was 114/56. Urine: sp. gr. 1.010 to 1.021 and occasional granular casts. Hemoglobin, 10.4 gm.; 3.4 million red cells. The white blood count was 7900 per c.mm. with 4% immature neutrophils. The Kline test was 3+ on 2 occasions, but the Wassermann was negative. The red cell sedimentation rate was elevated. Blood cultures were negative.

The joint pains and stiffness gradually disappeared during a month in the hospital. Five months later the patient was readmitted with pain in the left chest and fever. Her gums were spongy and bled easily. The liver edge was 3 finger-breadths down. In December 1937 a maculopapular rash with butterfly distribution appeared on the face, gradually fading after a month. Six months later, after exposure to sunlight, the joint pains recurred and there was a transient diplopia and low grade fever. Weakness was progressive thereafter and various joints became swollen, hot, and tender and there were frequent epistaxes. The temperature rose; the spleen was palpable. In February 1939 an abscess developed about the right elbow and pericarditis with effusion appeared. These conditions cleared, the temperature returned to normal, and a weight gain occurred during the summer of 1939. In September, however, the patient was readmitted to the hospital with a rough systolic murmur over the whole precordium and signs of chronic passive congestion. The course was rapidly downhill with terminal convulsions.

Histologic examination showed intimal hyaline material in the splenic arteries with many megakaryocytes and evidence of myelopœsia; hyperplasia of the lymph nodes without activation centers; chronic fibrous pericarditis; a chronic type of focal, chiefly subcapsular, interstitial nephritis with hyalinized thrombi. No sections were made of the heart valves. No periarteritis or focal interstitial lesions were seen in the kidney.

Anatomic Diagnosis. Atrophic dermatitis of the left pinna and superficial crusted lesions of the skin of both hands and knees; bronchopneumonia with acute arteritis of the vessels of the lungs; vegetative endocarditis (mitral, tricuspid, and aortic leaflets and mural); obliteration of the pericardial cavity; thrombi in the small arteries of the myocardium; small focal scars of the myocardium; focal interstitial and glomerulonephritis; chronic hyperplasia of the spleen; central necrosis of the liver; petechiæ of the skin of the hands, legs, and trunk.

CASE 4.—E. P., a 24-year-old, single American woman, was admitted to the hospital in January 1939 complaining of a facial eruption for 5 months. The skin lesion had appeared on the nose and spread to assume a butterfly shape. Two months before admission an ultra-violet treatment had been received; 2 days thereafter the lesion became larger and the eyelids swollen; and afternoon fever developed and a weight loss occurred.

Physical examination showed a chronically ill woman with a temperature of 38° C. The eyelids were edematous. There was an angry, red symmetrical lesion over the bridge of the nose reaching to the forehead and eyebrows, scaly in places. On the hands were isolated, blotchy, red areas which faded on pressure. On the hard and soft palates were raised, red, indurated areas which seemed to arise in petechial hemorrhages. The cervical and axillary and inguinal nodes showed shotty enlargement. Urine: sp. gr. 1.004–1.014 and 1+ albumin. Hemoglobin, 11.5 gm.; with 3.6 million red cells. The white blood count was 2300 (19% immature neutrophils). The blood Kline test was negative, blood urea nitrogen normal. The red cell sedimentation rate was normal. Blood cultures were negative.

The hospital course over a period of 5 weeks was one of progressive weakness with irregular fever. There was, however, no weight loss. The skin lesions on the face regressed slightly. The lesions on the palate increased in size and became painful but never ulcerated or bled. During the sixth week in tthe hospital bronchopneumonia developed. The patient died 2 weeks later.

Histologic examination showed fibrous and intimal thickening in the splenic arteries; hyperplasia of the lymph nodes—no activation centers were seen; endothelial proliferation of some tufts in the kidney and in many glomeruli definite hyaline thickening producing the "wire-loop" appearance; a few eosinophilic thrombi in glomerular capillaries. No periarteritis or glomerulonephritis was seen in the kidneys. No changes were seen in the mitral or tricuspid valves. There was very early pericarditis.

Anatomic Diagnosis. General atrophic dermatitis; serofibrinous pleurisy; bronchopneumonia of both lower lobes; slight fibrinous pericarditis; moderate edema of the perirenal and perivesical tissues; slight hyperplasia of the para-aortic and mesenteric nodes; passive congestion of the spleen and liver, and a calcified nodule in the liver.

CASE 5.—M. R., a 20-year-old, single woman of Italian parentage, was first admitted to the hospital in July 1939 complaining of arthritis in various joints for over 2 years. In the summer of 1937 there was sudden onset of severe joint pains in both hands; 2 months later swelling of the hand joints began and persisted. Subsequently the patient was confined to bed on several occasions because of involvement of the other joints.

Physical examination showed a well-nourished young woman with generalized lymphadenopathy. There was spindle-shaped swelling of the interphalangeal joints of the hands and third right toe. There were signs of a small amount of fluid in the right knee joint. The blood pressure was 115/70. The urine showed a specific gravity of 1.010–1.027 and a trace of albumin. The hemoglobin was 10.6 gm. The red blood count was 3.6 million. The white blood count was 3900 with 28% immature polynuclears. The blood Kline test was ± at one time, 3+ at another; the blood Wasser-

mann was anticomplementary. The red cell sedimentation rate was elevated. Blood cultures were negative. Biopsy of an axillary lymph node was interpreted as showing early lymphosarcoma but Hodgkin's disease was also felt to be a possibility. Roentgen ray treatments were given. The lymph nodes decreased markedly in size and the joint pains disappeared. After a week, however, a sharp pain in the lower left chest developed with night sweats and fever and edema of the face and neck appeared. The anterior cervical and submental nodes became enlarged, soft, and tender. A second series of Roentgen ray treatments was given 2 weeks after the first, but was discontinued because of evident signs of disseminated lupus erythematosus, the skin rash having occurred with butterfly distribution on the face. Biopsy of a skin lesion of the arm showed marked lymphocytic infiltration about the small vessels felt to be compatible with lupus but not diagnostic. Within a week the fever rose, the skin lesions cleared, respirations became labored and the voice hoarse. Laryngoscopy showed diffuse swelling of the vocal cords: tracheotomy was done. A terminal bronchopneumonia developed.

Anatomic Diagnosis. Atrophic dermatitis of the face, neck, and shoulders; bronchitis and bronchopneumonia; serous pleural effusion on the left; fibrinous pericarditis and ascites; edema of the lower extremities, abdominal wall, gastro-intestinal tract, retro-peritoneal tissues, and mediastinal structures of the face and neck; hyperplasia of the nodes in the cervical, axillary and abdominal regions; arthritis of the fingers, knees, and elbows; hyperplasia of the lymphoid tissue of the ileum and acute enteritis with ulceration.

Histologic examination showed fibrous thickening of the arteries of the spleen; hyperplasia of lymph nodes with numerous small activation centers; in the kidney many tufts with marked hyaline thickening—"wire-loop" lesions, and some eosinophilic thrombi; very early fibrinous pericarditis. The mitral valve was normal. No periarteritis or glomerulonephritis was seen.

Case 6.—M. S., a 27-year-old, married American woman, was first admitted to the hospital in February 1940 complaining of attacks of stiffness in the arms and legs for 4 months. In 1936 a raised, dry, red rash covered her nose and cheeks and spread to her chin. This improved slightly under light treatment but became more severe during a pregnancy in that year. One year before admission it was noted that the hands and feet, when exposed to cold, became white and pinched distally and purplish proximally. Six months before admission intermittent stabbing pains in the shoulder blades began. Two months later the fingers, arms, and legs became stiff at intervals, sometimes with fever. The patient was observed at another hospital where pericarditis with effusion was diagnosed. Biopsy of the deltoid muscle there showed periarteritis and perivasculitis consistent with disseminated lupus erythematosus. Sulfanilamide was given with improvement for a time. After a month, stiffness of the extremities recurred and fever set in. There had been a weight loss of 27 pounds in the year.

Physical examination on admission showed a dry, scaling, irregularly confluent lesion, slightly raised and brownish, over the chin and lips. There was an irregular pink-red macular eruption over the forearms, chest, and knees. There was a diastolic gallop rhythm over the mitral area. The second pulmonic sound was markedly accentuated. The blood pressure was 110/84. The hands and feet were cold and of a pale lavender hue. The range of movements of the joints was restricted. Urine: sp. gr. 1.009–1.025, an occasional trace of albumin, and 3 to 5 red blood cells per high power field. Hemoglobin, 9.9 gm.; the red blood count 3.7 million. The white blood count was 5000 (52% immature neutrophils and 5% eosinophils). The blood Kline test was negative. The blood urea nitrogen was

normal. The red cell sedimentation rate was elevated. Blood cultures were negative.

In the hospital the macular rash faded promptly. Several attacks of abdominal pain occurred. A vesicular eruption appeared on the roof of the mouth and tongue. A deep ulceration was felt in the hollow of the sacrum. There was an irregular fever. Gradual weight loss and progressive weakness occurred. After an epileptiform convulsion, the patient died in circulatory failure during the seventh week in the hospital.

Histologic examination showed massive lymphocytic infiltration between the venous endothelium and the trabeculæ in many places in the spleen. There was very early fibrinous pericarditis. The mitral valve showed no change. There was a mild myocarditis of the periarterial type. At the base of the tricuspid valve on the ventricular wall were small thrombotic masses. The kidneys showed chronic pyelitis with central abscesses and pus in the tubules. No "wire-loop" lesions were seen.

Anatomic Diagnosis. Focal atrophy of the skin of the face, right ear, chest, and shoulder; edema of the lungs with hemorrhage; fibrous adhesions between visceral and parietal layers of the pleura and peritoneum with hydropericardium and bilateral hydrothorax; acute pyelonephritis on the left; passive congestion of the spleen and liver; colitis with multiple large ulcers in the rectum and descending colon and extension of the inflammation to the parietal tissues; patent foramen ovale.

Discussion. All 6 cases were in women aged 20–36 years. Three of the patients were of American parentage; 1 was of Italian, 1 of Polish, and 1 of Swedish extraction. Four were married and had had 1 or 2 children. The occupational histories were not remarkable. One patient had had a tuberculous neck gland at the age of 10 years; 5 had had tonsillectomies.

The duration of the joint pains varied from 6 months to $6\frac{1}{2}$ years. The "butterfly" skin rash was noted in all, in one 18 days before death, in another persisting for 11 years before death. All of the patients had fever at times during periods of 3 weeks to 4 years. All lost considerable weight. One patient showed postneuritic optic atrophy. Splenomegaly was found in 2 patients. The heart findings were varied. All the patients showed some tachycardia, usually paralleling the temperature rises. In the one case, however, which showed at autopsy verrucous endocarditis, no cardiac lesion was diagnosed clinically.

The urine showed from a trace to 2+ albumin in all cases, with red cells and casts in each case at one time or another. All showed slight to moderate secondary anemia. The white cell count was under 5000 in 2 cases, 5000–10,000 in 3 cases, and 12,000 in 1 case. The blood Wassermann test was negative in 4 cases, anticomplementary in one case, and 3+ at times in 1 case in whom no history or other findings suggestive of syphilis were found.

The hospital course was marked by progressive weakness in each case. The duration of the hospital stay varied from 42 days to 29 months. Bronchopneumonia was a terminal event in 5 cases, complicated in one of these by congestive heart failure. One patient developed convulsions and circulatory failure just before death.

TABLE 1.—BRIEF SUMMARY OF CERTAIN FINDINGS OF INTEREST IN 6 AUTOPSIED CASES OF DISSEMINATED LUPUS ERYTHEMATOSUS

Case	History and clinical findings					Chief gross findings	Autopsy, chief histological findings			
	Age	Duration of rash	Duration of joint pains	Duration of fever	Misc.		Spleen	Lymph nodes	Heart	Kidneys
1. EW	36	9 yrs.	2 yrs.	9 mos.	Otitis media	Chr. dermatitis; chr. pericarditis; ac. and chr. arthritis (knee); tb. of mesenteric nodes	....	Hyperplasia without activation centers†	Chr. pericarditis; no mitral lesion	Agonal degeneration of tubules; hyperemia*
2. BH	28	11 mos.	18 mos.	11 mos.	Cystitis; abscess of knee and hip	Lupus erythem. with hem. serofibrinosis, pericarditis; bilat. pyelonephritis; ac. and chr. arthritis; tb. of spleen and ly. nodes	Subendothelial lymphocytic infiltration of trabecular veins	Disseminated tbc.	Pericarditis; no mitral lesion	Some swollen glomerular* tufts; chr. pyelonephritis
3. GH	30	Few days	6 yrs.	3 yrs.	Abscess of elbow	Atrophic dermatitis; chr. pericarditis; veg. endocarditis; myocardial scars	Intimal thickening of arteries	Hyperplasia	Chr. pericarditis (valves not sectioned)	Chronic subcapsular interstitial nephritis; a few minimal hyaline "wire-loop" lesions; rare hyaline thrombi
4. EP	24	6 mos.	6 mos.	3½ wks.	Calcif. tb. nodule-liver	Atrophic dermatitis; fibrinous pericarditis	Fibrous and intimal hyaline thickening of arteries	Hyperplasia	Very early pericarditis; no mitral or tricuspid lesions	Typical "wire-loop" lesions; eosinophilic thrombi
5. MR	20	3 days	2 yrs.	1 mo.	Lymphosarcoma diagnosed from biopsy; roentgen-ray given	Atrophic dermatitis; fibrinous pericarditis; polyarthritis	Fibrous thickening of arteries	Hyperplasia with many small activation centers	Very early fibrinous pericarditis; no mitral lesion	Marked "wire-loop" lesions; eosinophilic thrombi
6. MS	27	4 yrs.	6 mos.	5 mos.	....	Atrophy of skin; pleural and peritoneal fibrous adhesions; ac. pyelonephritis and colitis; hydropericard. and hydrothorax	Subendothelial lymphocytic infiltration—trabecular veins	Hyperplasia	Very early fibrinous pericarditis; Libman-Sacks type of endocarditis of tricuspid	Chronic pyelitis;* central abscess and pus in tubules

* No specific lupus changes.
† Grossly calcified tb. nodules in mesenteric nodes.

Postmortem examination showed fibrin about the pleural and pericardial surfaces in all 6 cases; infiltration was, however, not seen histologically in the pericardium in 3 of these. In only one case was endocarditis detected grossly; that was verrucous in type, involving the mitral and tricuspid valves, the aortic leaflets, and the mural endocardium of the left ventricle. All 6 cases showed some evidence of kidney abnormality, chronic pyelitis with abscesses being present in one case. There was lymph node hyperplasia in all cases. The liver and spleen showed grossly chronic passive congestion. There were hemorrhages in the intestinal mucosa in 2 cases, ulceration in 2 others. There were evidences of synovial joint changes in 2 cases. Endocarditis was not confirmed histologically in the one case where it was seen grossly because sections were not made of the valves. Endocarditis, typical of the early Libman-Sacks type, was identified on the tricuspid valve on one other case, the only one in which that valve was sectioned; this lesion was not seen grossly and was unaccompanied by histologic evidence of pericarditis or specific renal lesions. Histologically the lymph nodes showed only hyperplasia, usually with no germinal centers. The spleen showed hemosiderin in 1 case, megakaryocytes and myelopoiesis in another, and perivenous infiltrate in the trabeculæ of 2 cases. The kidneys showed "wire-loop" lesions in 3 cases. No periarteritis or diffuse glomerulonephritis was seen. One case showed a curious subcapsular interstitial and glomerular nephritis with only focal disseminated lesions. No case showed the curious refractile thrombi or precipitate in glomerular capillaries.

Certain significant points are listed in Table 1, page 40.

Summary. The clinical, laboratory, and autopsy findings in 6 cases of disseminated lupus erythematosus observed at the New York Hospital between 1936 and 1940 are reported.

No common etiologic basis was observed in these 6 young women. Study of the diseased tissues cast no light on the pathogenesis.

While vascular lesions were observed, none of the cases resembled periarteritis nodosa. Noteworthy was the frequent association with acute and chronic arthritis and with pericarditis.

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RHEUMATOID ARTHRITIS AND RHEUMATIC HEART DISEASE IN AUTOPSIED CASES.

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Lesions identical with some of the rheumatic fever changes in the heart have recently been reported to be present in a little over half (56%) of patients (25) dying with apparently characteristic rheumatoid arthritis.[1] An analysis and review of the literature concerning this relationship reveals that except for the above paper, little pathologic information concerning cardiac findings in rheumatoid arthritis is available. Numerous clinical reports of the coexistence or relationship of these two diseases in the same patients or in different groups of patients have not served to clarify the situation.[4,7,8,9,11] Pathologic studies on the subcutaneous nodules which occur in these two conditions have shown somewhat similar fundamental changes.[6,10] In more recent studies, Collins[5] and Bennett, Zeller and Bauer[3] have drawn attention to certain structural and cytologic dissimilarities between these subcutaneous lesions. On the basis of morphologic data, it was usually possible for the latter authors to distinguish the nodules occurring in rheumatic fever patients from the nodules occurring in patients with rheumatoid arthritis. Because of these observed differences it was suggested that the lesions may be due to different agents.

Since the question of the coëxistence or relationship of these two diseases is at present in doubt, it seemed worthwhile to review the autopsied cases of rheumatoid arthritis which are available at the Robert Breck Brigham Hospital. The material presented should be regarded as added information rather than as an attempt to settle the discussion. It is further hoped that eventual clarification of these two disease entities and their interrelationship, if any, will speed the search for the causative factor or factors concerned.

Materials and Methods. Twenty-three patients with definite rheumatoid arthritic changes in their joints have been studied at autopsy at the Robert Breck Brigham Hospital since 1914. The course and clinical findings were characteristic of rheumatoid arthritis with chronic joint pain and swelling producing progressive crippling over a period of years. In some instances the presence or absence of arthritic activity at the time of death could not be definitely ascertained but in each case the clinical and roentgenographic evidence made inescapable the definite diagnosis of rheumatoid arthritic crippling of some years' duration. All cases in which there was any question of another clinical cause of joint deformity have been rigidly excluded. The history of the patients and the temporal relationships of the two disorders have been reviewed and tabulated.

The pathologic information has been obtained in most instances from the protocols of the gross and histologic findings. The criterion for the

gross diagnosis of rheumatic heart disease was gross valvular change such as thickening of the leaflet edges and retraction of the leaflet edge by the shortened chordæ tendinæ. The presence of active typical Aschoff bodies was used as the histologic criterion for the diagnosis of active rheumatic fever. Dr. J. B. Hazard performed the autopsies on Cases 7, 13 and 23 (Table 1) and reviewed this material. Four of the autopsies, Cases 3, 5, 14 and 22 (Table 1), were performed by Dr. G. A. Bennett and he kindly reviewed the material from them.

Results. The pathologic findings in the joints were well advanced in most instances as the duration of rheumatoid arthritis varied from 1 to 25 years with an average duration of over 11 years. In all patients several joints were involved grossly and showed fusiform swelling or an ankylosing deformity. When complete ankylosis was present it was either fibrous or bony with disappearance of the joint space. Joints with fusiform swelling showed at autopsy thickened reddish synovial membrane and a doughy thickening of the articular capsule and periarticular tissues. Pannus formation extending centrally over the articular surfaces of the joint cartilage was seen in each instance. The cartilage was pitted and thinned under the pannus. In the patients with joint deformity of long standing (usually over 7 years), the edges of the joint surfaces showed some chondro-osseous proliferation.

Microscopic studies of sections through the synovia and the articular capsule usually showed an inflammatory process of moderate severity. The synovial lining cells are sometimes oriented in a vertical direction. The subsynovial layers are somewhat edematous and infiltrated with lymphocytes and other forms of leukocytes, including neutrophils. There are scattered small collections of lymphocytes centered around blood-vessels. In the more active cases acute inflammatory lesions involving small blood-vessels are also noted and occasionally these seem thrombosed and often a considerable amount of acidophilic hyaline fibrin or fibrin-like material is found on or within the synovial lining tissues. Sections from the articular surfaces show a layer of vascularized and chronically inflamed connective tissue (pannus) extending over the cartilage and producing dissolution and thinning of this joint element. The underlying bone is atrophic. In the patients with arthritis of long standing, microscopic studies of the joint surfaces show that they are joined together by dense fibrous tissue pannus that is moderately infiltrated diffusely and in focal areas with lymphocytes. In some patients, this connective tissue bridge is undergoing calcification and even bone formation. The patients with the Strümpell-Marie variety of rheumatoid arthritis showed fundamentally the same pathologic processes in the joints of the spine with calcification of the spinal ligaments in all our cases. The shortest duration of this disease was 7 years in our group.

Table 1 summarizes the clinical facts and the pathologic findings in the hearts of these patients.

TABLE 1.—CLINICAL DATA AND PATHOLOGIC OBSERVATIONS ON THE HEARTS OF 23 AUTOPSIED CASES OF RHEUMATOID ARTHRITIS.

No.	Sex.	Clinical diagnosis.*	Age at onset of R.A. (yrs.).	Age at death (yrs.).	History of rheumatic fever.	Age at time of R.F. (yrs.).	Age at time of cardiac diagnosis (yrs.).	Age at time of cardiac symptoms (yrs.).	Weight (gm.).	Pathologic cardiac findings at autopsy.			Cause of death.
										Valves involved.	Pericardium.	Histologic.	
1	F	R.A.°-R.H.D.°	31	53	..	..	52	Never	400	Mitr. thickening and retraction	Active adherent throughout	Healing inflammatory pericarditis	Br. pneum., pul. tubere.
2	F	R.A.-R.H.D.	(20-25)? 45	49	..	..	40	40	485	Mitr. sten.	Healed adherent patch	Inact. rheum. myocard. and valv. changes	Mult. cbr. emboli, subac. bact. endocarditis.
3	M	R.A.-R.H.D. (Strümpell-Marie)	24	35	+	13	13	Never	360	Sl. mitr. sten., aortic sten.	Normal	Inact. rheum. myocard. and valv. changes	Cbr. hem., subac. bact. endocarditis.
4	M	R.A.-R.H.D. (Strümpell-Marie)	41	51	..	..	48	51	610	Aortic sten.	Normal	Inact. rheum. myocard. and valv. changes	Cardiac failure.
5	F	R.A.	45	69	..	..	Postmortem	Never	530	Sl. mitr. sten.	Normal	Inact. rheum. valv. changes	Br. pneum.
6	M	R.A.	34	42	..	..	Postmortem	Never	Sl. enlarged	Sl. mitr. sten.	Normal	Not reported	Cerebral thrombosis.
7	F	R.A. (Still's)	11	12	..	..	(Adhesive pericarditis) 12	12	340 (3 × normal)	None	Healing adherent throughout	No rheum. changes	Cardiac failure, acute staph. endocarditis.
8	F	R.A.	47	72	..	..	....	..	260	None	Healed adherent throughout	No rheum. changes	Br. pneum.
9	M	R.A. (Strümpell-Marie)	31	42	+	5 (chorea)	....	..	310	Art. scler. plaques, aortic mitr. pulmon.	Normal	No rheum. changes	Amyloidosis, nephritis.
10	F	R.A.	52	60	..	..	....	..	190	None	Normal	No rheum. changes	Purulent peritonitis.
11	F	R.A.	36	44	..	..	....	..	360	None	Normal	No rheum. changes	Rupt. esoph. varix, cirrhosis of liver.
12	F	R.A.	35	49	..	..	....	..	170	None	Normal	No rheum. changes	Postop. shock.
13	M	R.A.	23	35	..	..	....	..	310	None	Normal	No rheum. changes	Postop. staph. septicemia.
14	F	R.A. (Strümpell-Marie)	24	41	..	..	37 Patent ductus arteriosus	Never	300	None	Normal	No rheum. changes, patent duc. arter.	Carcinoma of breast.
15	F	R.A.	42	59	..	..	....	..	Normal	None	Normal	No rheum. changes	Volv., br. pneum.
16	M	R.A.	25	32	+	17	....	..	290	None	Normal	Not reported	Chr. glom.-nephritis.
17	M	R.A.	37	44	+	15	....	..	410	None	Normal	No rheum. changes	Erysipelas, amyloidosis
18	F	R.A.	69	76	..	..	....	..	325	None	Normal	No rheum. changes	Carcinoma of uterus.
19	M	R.A. (Strümpell-Marie)	21	31	..	..	....	..	250	None	Normal	No rheum. changes	Staph. septicemia.
20	M	R.A. (Strümpell-Marie)	51	58	..	..	....	..	300	None	Normal	No rheum. changes	Postop. fat embolus.
21	M	R.A.	25	37	..	..	....	..	330	None	Normal	No rheum. changes	Chr. nephr., br. pneum.
22	F	R.A. (Still's)	9	27	..	..	....	..	330	None	Normal	No rheum. changes	Pul. tubere., br. pneum.
23	M	R.A.	15	23	..	..	....	..	280	None	Normal	No rheum. changes	General. amyloidosis.

Gross Lesions in the Heart. Six (Cases 1 to 6) of 23 cases of rheumatoid arthritis had cardiac changes at autopsy characteristic of those usually found subsequent to rheumatic fever with cardiac involvement. Four of these 6 cases showed varying degrees of mitral stenosis and 1 had aortic stenosis. Case 3 had slight mitral stenosis and moderate aortic stenosis of 22 years' standing. The weight of the hearts of these patients varied from 360 to 610 gm. with an average weight of 477 gm.

Cases 1 and 2 also had gross pericardial involvement. Case 1 showed an active adherent pericarditis obliterating the pericardial space while Case 2 had a healed adherent patch of pericarditis.

Two additional patients (Cases 7 and 8) had adhesive non-constricting pericarditis. One (Case 7) was healing and occurred concomitantly with very active rheumatoid arthritis (Still's disease) in a 12-year-old girl; the pericardial and pleuropericardial adhesions produced cardiac hypertrophy (340 gm.) but there were no endocardial changes before or after death and multiple sections of the pericardium and myocardium showed no Aschoff nodules or other pathognomonic changes of active rheumatic fever. In the second (Case 8) the pericarditis was found to be healed and thinly fibrous in a 72-year-old woman with no history of rheumatic fever; in this case the heart weighed 260 gm., here again rheumatic stigmata were absent.

The cardiac lesions not consistent with those of rheumatic fever found in 13 of the remaining 14 cases were mild arteriosclerotic changes in the older patients and consistent with their age. In none of these were the cardiac changes lethal. The remaining patient (Case 14) had a symptomless congenital ductus arteriosus, diagnosed antemortem.

Histologic Lesions. In no case did the histologic examination disclose active or inactive rheumatic changes in the tissue which might not have been apparent at the gross examination. In only 1 of the 6 cases with gross cardiac changes did the histologic examination reveal activity of the lesions with changes that may have been due to active rheumatic fever. Case 1 had at autopsy a healing inflammatory pericarditis in the presence of active pulmonary tuberculosis and terminal bronchopneumonia. The activity of this pericarditis might have been due to the pulmonary infection or the rheumatic fever state, but neither Aschoff nodules or tubercles were found in the sections. Therefore it was not possible to conclude more than that this lesion might represent an active rheumatic fever change, but that it may be entirely dependent upon the pulmonary infection. The fact that 3 of Cases 2, 3, 4 and 5 had terminal pulmonary infection without even questionable active rheumatic fever changes in the tissues could be interpreted to favor the possibility that the active tissue changes in Case 1 might be due to rheumatic fever. In Case 5 there was healed rheumatic

mitral valve thickening with terminal platelet deposits, but no active rheumatic lesions were seen. Histologic examination revealed inactive rheumatic fever changes in the valve leaflets and myocardium in the other cases (Cases 2, 3 and 4, Table 1).

Clinical Observations and Comment. There were 12 female and 11 male patients in this series, and of the latter, 5 had a Strümpell-Marie type of involvement. Three of each sex had rheumatic changes in the heart at autopsy. Rheumatoid arthritics of the usual type had about the same frequency of cardiac changes as did the Still or Strümpell-Marie varieties.

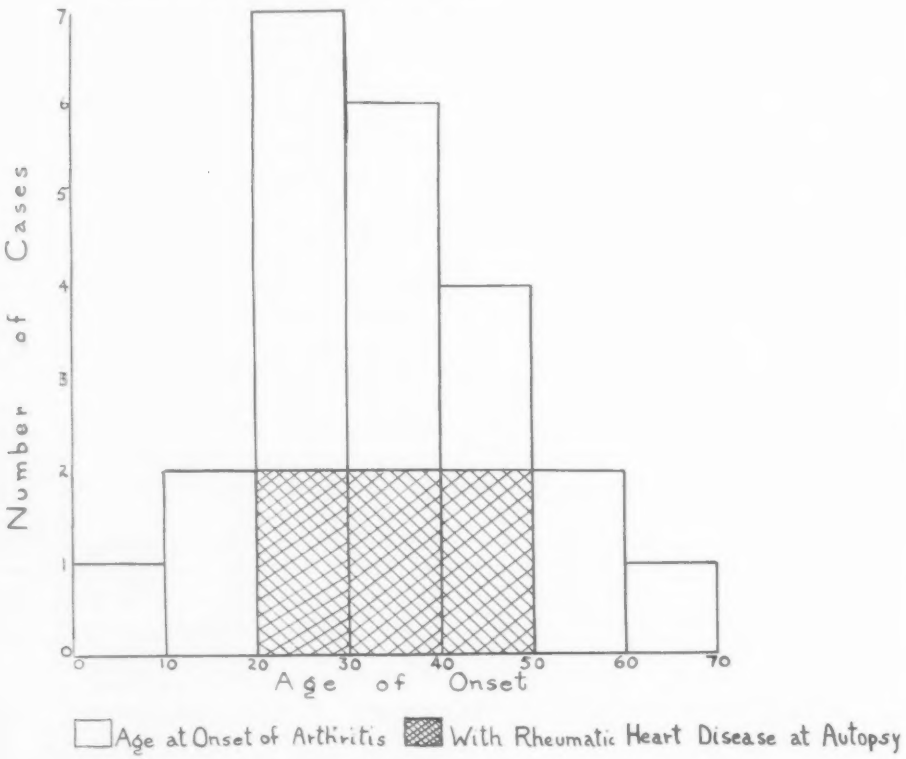

FIG. 1.—Incidence of rheumatic heart disease at autopsy as related to the age of onset of rheumatoid arthritis.

Figure 1 reveals no tendency for the age of onset to have any effect on the incidence of cardiac changes due to rheumatic fever. The average age of onset of rheumatoid arthritis of patients without cardiac changes was 29, 3 years less than the average for those with cardiac changes, 32 years.

Of the 6 cases with rheumatic cardiac changes 3 had a rapid onset of their arthritis, 1 moderately rapid and 2 insidious.

Three patients (Cases 3, 16 and 17) gave a definite clinical history of rheumatic fever but only Case 3 had subsequent rheumatic cardiac changes demonstrable at death and these were inactive. Correcting the statistics by the exclusion of this patient, 5 of 22 patients (22%) dying with rheumatoid arthritic changes in the joints had rheumatic cardiac changes at autopsy unexplained by a known previous attack of rheumatic fever. This, while an impressive finding, is less than one-half the percentage found by Baggenstoss and Rosenberg[1] in a series of 25 cases, even when their series is corrected for the same factor.

While a series of this size does not lend itself to statistical analysis, there are three important factors which appreciably temper the importance of finding 22% with rheumatic cardiac changes at autopsy. First, in one-half of the patients in which there were rheumatic changes at autopsy the heart was the center of interest ante- and postmortem. Two died of subacute bacterial endocarditis superimposed on inactive rheumatic vulvulitis and 1 of cardiac decompensation resulting from aortic stenosis and cardiac hypertrophy. Only 3 of 19 patients (15%) dying of non-cardiac causes had rheumatic cardiac changes at autopsy. Second, 4 of this group of 23 patients (17%) had clinical signs of rheumatic heart disease antemortem. This is a significantly larger proportion than the 7% found by Dawson and Tyson[7] and the 5% found in our clinic[2] in 100 consecutive rheumatoid arthritic patients. Third, as clinical activity of the rheumatoid arthritis was usually present at the time of death, it seems unusual, if the two diseases are related, that only 1 case in 23 (4%) showed signs of active rheumatic fever and even in this one, these signs were not pathognomonic but only suggestive. These observations appear to make this group selected rather than usual, but why they should come to autopsy more than an unselected group is not clear, unless the type of fatal illness led to hospitalization and more intensive study. It is well known that sufferers of rheumatoid arthritis do not die of this disease and that many die of other causes in nursing homes or in their own homes where facilities for autopsy examination are not readily accessible.

Summary and Conclusions. Of 23 autopsied cases of rheumatoid arthritis, 6 were found to have changes in the heart valve leaflets and myocardium similar to those that usually follow rheumatic fever. The histologic lesions of 1 of these 6 could possibly be considered active and 5 were inactive in character. Excluding 1 patient because of definite rheumatic fever and rheumatic heart disease present in childhood, 22% had rheumatic cardiac lesions. The factors of accentuation on cardiac death, the relatively large group with cardiac changes antemortem as compared to control groups, and the small number of cases (possibly 1) with active rheumatic fever lesions have been pointed out. The rheumatoid arthritics in this apparently selected series have a rather high incidence of cardiac

mann was anticomplementary. The red cell sedimentation rate was elevated. Blood cultures were negative. Biopsy of an axillary lymph node was interpreted as showing early lymphosarcoma but Hodgkin's disease was also felt to be a possibility. Roentgen ray treatments were given. The lymph nodes decreased markedly in size and the joint pains disappeared. After a week, however, a sharp pain in the lower left chest developed with night sweats and fever and edema of the face and neck appeared. The anterior cervical and submental nodes became enlarged, soft, and tender. A second series of Roentgen ray treatments was given 2 weeks after the first, but was discontinued because of evident signs of disseminated lupus erythematosus, the skin rash having occurred with butterfly distribution on the face. Biopsy of a skin lesion of the arm showed marked lymphocytic infiltration about the small vessels felt to be compatible with lupus but not diagnostic. Within a week the fever rose, the skin lesions cleared, respirations became labored and the voice hoarse. Laryngoscopy showed diffuse swelling of the vocal cords: tracheotomy was done. A terminal bronchopneumonia developed.

Anatomic Diagnosis. Atrophic dermatitis of the face, neck, and shoulders; bronchitis and bronchopneumonia; serous pleural effusion on the left; fibrinous pericarditis and ascites; edema of the lower extremities, abdominal wall, gastro-intestinal tract, retro-peritoneal tissues, and mediastinal structures of the face and neck; hyperplasia of the nodes in the cervical, axillary and abdominal regions; arthritis of the fingers, knees, and elbows; hyperplasia of the lymphoid tissue of the ileum and acute enteritis with ulceration.

Histologic examination showed fibrous thickening of the arteries of the spleen; hyperplasia of lymph nodes with numerous small activation centers; in the kidney many tufts with marked hyaline thickening—"wire-loop" lesions, and some eosinophilic thrombi; very early fibrinous pericarditis. The mitral valve was normal. No periarteritis or glomerulonephritis was seen.

Case 6.—M. S., a 27-year-old, married American woman, was first admitted to the hospital in February 1940 complaining of attacks of stiffness in the arms and legs for 4 months. In 1936 a raised, dry, red rash covered her nose and cheeks and spread to her chin. This improved slightly under light treatment but became more severe during a pregnancy in that year. One year before admission it was noted that the hands and feet, when exposed to cold, became white and pinched distally and purplish proximally. Six months before admission intermittent stabbing pains in the shoulder blades began. Two months later the fingers, arms, and legs became stiff at intervals, sometimes with fever. The patient was observed at another hospital where pericarditis with effusion was diagnosed. Biopsy of the deltoid muscle there showed periarteritis and perivasculitis consistent with disseminated lupus erythematosus. Sulfanilamide was given with improvement for a time. After a month, stiffness of the extremities recurred and fever set in. There had been a weight loss of 27 pounds in the year.

Physical examination on admission showed a dry, scaling, irregularly confluent lesion, slightly raised and brownish, over the chin and lips. There was an irregular pink-red macular eruption over the forearms, chest, and knees. There was a diastolic gallop rhythm over the mitral area. The second pulmonic sound was markedly accentuated. The blood pressure was 110/84. The hands and feet were cold and of a pale lavender hue. The range of movements of the joints was restricted. Urine: sp. gr. 1.009–1.025, an occasional trace of albumin, and 3 to 5 red blood cells per high power field. Hemoglobin, 9.9 gm.; the red blood count 3.7 million. The white blood count was 5000 (52% immature neutrophils and 5% eosinophils). The blood Kline test was negative. The blood urea nitrogen was

normal. The red cell sedimentation rate was elevated. Blood cultures were negative.

In the hospital the macular rash faded promptly. Several attacks of abdominal pain occurred. A vesicular eruption appeared on the roof of the mouth and tongue. A deep ulceration was felt in the hollow of the sacrum. There was an irregular fever. Gradual weight loss and progressive weakness occurred. After an epileptiform convulsion, the patient died in circulatory failure during the seventh week in the hospital.

Histologic examination showed massive lymphocytic infiltration between the venous endothelium and the trabeculæ in many places in the spleen. There was very early fibrinous pericarditis. The mitral valve showed no change. There was a mild myocarditis of the periarterial type. At the base of the tricuspid valve on the ventricular wall were small thrombotic masses. The kidneys showed chronic pyelitis with central abscesses and pus in the tubules. No "wire-loop" lesions were seen.

Anatomic Diagnosis. Focal atrophy of the skin of the face, right ear, chest, and shoulder; edema of the lungs with hemorrhage; fibrous adhesions between visceral and parietal layers of the pleura and peritoneum with hydropericardium and bilateral hydrothorax; acute pyelonephritis on the left; passive congestion of the spleen and liver; colitis with multiple large ulcers in the rectum and descending colon and extension of the inflammation to the parietal tissues; patent foramen ovale.

Discussion. All 6 cases were in women aged 20–36 years. Three of the patients were of American parentage; 1 was of Italian, 1 of Polish, and 1 of Swedish extraction. Four were married and had had 1 or 2 children. The occupational histories were not remarkable. One patient had had a tuberculous neck gland at the age of 10 years; 5 had had tonsillectomies.

The duration of the joint pains varied from 6 months to $6\frac{1}{2}$ years. The "butterfly" skin rash was noted in all, in one 18 days before death, in another persisting for 11 years before death. All of the patients had fever at times during periods of 3 weeks to 4 years. All lost considerable weight. One patient showed postneuritic optic atrophy. Splenomegaly was found in 2 patients. The heart findings were varied. All the patients showed some tachycardia, usually paralleling the temperature rises. In the one case, however, which showed at autopsy verrucous endocarditis, no cardiac lesion was diagnosed clinically.

The urine showed from a trace to 2+ albumin in all cases, with red cells and casts in each case at one time or another. All showed slight to moderate secondary anemia. The white cell count was under 5000 in 2 cases, 5000–10,000 in 3 cases, and 12,000 in 1 case. The blood Wassermann test was negative in 4 cases, anticomplementary in one case, and 3+ at times in 1 case in whom no history or other findings suggestive of syphilis were found.

The hospital course was marked by progressive weakness in each case. The duration of the hospital stay varied from 42 days to 29 months. Bronchopneumonia was a terminal event in 5 cases, complicated in one of these by congestive heart failure. One patient developed convulsions and circulatory failure just before death.

TABLE 1.—BRIEF SUMMARY OF CERTAIN FINDINGS OF INTEREST IN 6 AUTOPSIED CASES OF DISSEMINATED LUPUS ERYTHEMATOSUS

Case	History and clinical findings					Chief gross findings	Autopsy, chief histological findings			
	Age	Duration of rash	Duration of joint pains	Duration of fever	Misc.		Spleen	Lymph nodes	Heart	Kidneys
1. EW	36	9 yrs.	2 yrs.	9 mos.	Otitis media	Chr. dermatitis; chr. pericarditis; ac. and chr. arthritis (knee); tb. of mesenteric nodes	....	Hyperplasia without activation centers†	Chr. pericarditis; no mitral lesion	Agonal degeneration of tubules; hyperemia*
2. BH	28	11 mos.	18 mos.	11 mos.	Cystitis; abscess of knee and hip	Lupus erythem. with hem. serofibrinosis, pericarditis; bilat. pyelonephritis; ac. and chr. arthritis; tb. of spleen and ly. nodes	Subendothelial lymphocytic infiltration of trabecular veins	Disseminated tbc.	Pericarditis; no mitral lesion	Some swollen glomerular* tufts; chr. pyelonephritis
3. GH	30	Few days	6 yrs.	3 yrs.	Abscess of elbow	Atrophic dermatitis; chr. pericarditis; veg. endocarditis; myocardial scars	Intimal thickening of arteries	Hyperplasia	Chr. pericarditis (valves not sectioned)	Chronic subcapsular interstitial nephritis; a few minimal hyaline "wire-loop" lesions; rare hyaline thrombi
4. EP	24	6 mos.	6 mos.	3½ wks.	Calcif. tb. nodule-liver	Atrophic dermatitis; fibrinous pericarditis	Fibrous and intimal hyaline thickening of arteries	Hyperplasia	Very early pericarditis; no mitral or tricuspid lesions	Typical "wire-loop" lesions; eosinophilic thrombi
5. MR	20	3 days	2 yrs.	1 mo.	Lymphosarcoma diagnosed from biopsy; roentgen-ray given	Atrophic dermatitis; fibrinous pericarditis; polyarthritis	Fibrous thickening of arteries	Hyperplasia with many small activation centers	Very early fibrinous pericarditis; no mitral lesion	Marked "wire-loop" lesions; eosinophilic thrombi
6. MS	27	4 yrs.	6 mos.	5 mos.	....	Atrophy of skin; pleural and peritoneal fibrous adhesions; ac. pyelonephritis and colitis; hydropericard. and hydrothorax	Subendothelial lymphocytic infiltration—trabecular veins	Hyperplasia	Very early fibrinous pericarditis; Libman-Sacks type of endocarditis of tricuspid	Chronic pyelitis;* central abscess and pus in tubules

* No specific lupus changes.
† Grossly calcified tb. nodules in mesenteric nodes.

Postmortem examination showed fibrin about the pleural and pericardial surfaces in all 6 cases; infiltration was, however, not seen histologically in the pericardium in 3 of these. In only one case was endocarditis detected grossly; that was verrucous in type, involving the mitral and tricuspid valves, the aortic leaflets, and the mural endocardium of the left ventricle. All 6 cases showed some evidence of kidney abnormality, chronic pyelitis with abscesses being present in one case. There was lymph node hyperplasia in all cases. The liver and spleen showed grossly chronic passive congestion. There were hemorrhages in the intestinal mucosa in 2 cases, ulceration in 2 others. There were evidences of synovial joint changes in 2 cases. Endocarditis was not confirmed histologically in the one case where it was seen grossly because sections were not made of the valves. Endocarditis, typical of the early Libman-Sacks type, was identified on the tricuspid valve on one other case, the only one in which that valve was sectioned; this lesion was not seen grossly and was unaccompanied by histologic evidence of pericarditis or specific renal lesions. Histologically the lymph nodes showed only hyperplasia, usually with no germinal centers. The spleen showed hemosiderin in 1 case, megakaryocytes and myelopoiesis in another, and perivenous infiltrate in the trabeculæ of 2 cases. The kidneys showed "wire-loop" lesions in 3 cases. No periarteritis or diffuse glomerulonephritis was seen. One case showed a curious subcapsular interstitial and glomerular nephritis with only focal disseminated lesions. No case showed the curious refractile thrombi or precipitate in glomerular capillaries.

Certain significant points are listed in Table 1, page 40.

Summary. The clinical, laboratory, and autopsy findings in 6 cases of disseminated lupus erythematosus observed at the New York Hospital between 1936 and 1940 are reported.

No common etiologic basis was observed in these 6 young women. Study of the diseased tissues cast no light on the pathogenesis.

While vascular lesions were observed, none of the cases resembled periarteritis nodosa. Noteworthy was the frequent association with acute and chronic arthritis and with pericarditis.

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† Grossly calcified tb. nodules in mesenteric nodes.

RHEUMATOID ARTHRITIS AND RHEUMATIC HEART DISEASE IN AUTOPSIED CASES.

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Lesions identical with some of the rheumatic fever changes in the heart have recently been reported to be present in a little over half (56%) of patients (25) dying with apparently characteristic rheumatoid arthritis.[1] An analysis and review of the literature concerning this relationship reveals that except for the above paper, little pathologic information concerning cardiac findings in rheumatoid arthritis is available. Numerous clinical reports of the coexistence or relationship of these two diseases in the same patients or in different groups of patients have not served to clarify the situation.[4,7,8,9,11] Pathologic studies on the subcutaneous nodules which occur in these two conditions have shown somewhat similar fundamental changes.[6,10] In more recent studies, Collins[5] and Bennett, Zeller and Bauer[3] have drawn attention to certain structural and cytologic dissimilarities between these subcutaneous lesions. On the basis of morphologic data, it was usually possible for the latter authors to distinguish the nodules occurring in rheumatic fever patients from the nodules occurring in patients with rheumatoid arthritis. Because of these observed differences it was suggested that the lesions may be due to different agents.

Since the question of the coëxistence or relationship of these two diseases is at present in doubt, it seemed worthwhile to review the autopsied cases of rheumatoid arthritis which are available at the Robert Breck Brigham Hospital. The material presented should be regarded as added information rather than as an attempt to settle the discussion. It is further hoped that eventual clarification of these two disease entities and their interrelationship, if any, will speed the search for the causative factor or factors concerned.

Materials and Methods. Twenty-three patients with definite rheumatoid arthritic changes in their joints have been studied at autopsy at the Robert Breck Brigham Hospital since 1914. The course and clinical findings were characteristic of rheumatoid arthritis with chronic joint pain and swelling producing progressive crippling over a period of years. In some instances the presence or absence of arthritic activity at the time of death could not be definitely ascertained but in each case the clinical and roentgenographic evidence made inescapable the definite diagnosis of rheumatoid arthritic crippling of some years' duration. All cases in which there was any question of another clinical cause of joint deformity have been rigidly excluded. The history of the patients and the temporal relationships of the two disorders have been reviewed and tabulated.

The pathologic information has been obtained in most instances from the protocols of the gross and histologic findings. The criterion for the

gross diagnosis of rheumatic heart disease was gross valvular change such as thickening of the leaflet edges and retraction of the leaflet edge by the shortened chordæ tendinæ. The presence of active typical Aschoff bodies was used as the histologic criterion for the diagnosis of active rheumatic fever. Dr. J. B. Hazard performed the autopsies on Cases 7, 13 and 23 (Table 1) and reviewed this material. Four of the autopsies, Cases 3, 5, 14 and 22 (Table 1), were performed by Dr. G. A. Bennett and he kindly reviewed the material from them.

Results. The pathologic findings in the joints were well advanced in most instances as the duration of rheumatoid arthritis varied from 1 to 25 years with an average duration of over 11 years. In all patients several joints were involved grossly and showed fusiform swelling or an ankylosing deformity. When complete ankylosis was present it was either fibrous or bony with disappearance of the joint space. Joints with fusiform swelling showed at autopsy thickened reddish synovial membrane and a doughy thickening of the articular capsule and periarticular tissues. Pannus formation extending centrally over the articular surfaces of the joint cartilage was seen in each instance. The cartilage was pitted and thinned under the pannus. In the patients with joint deformity of long standing (usually over 7 years), the edges of the joint surfaces showed some chondro-osseous proliferation.

Microscopic studies of sections through the synovia and the articular capsule usually showed an inflammatory process of moderate severity. The synovial lining cells are sometimes oriented in a vertical direction. The subsynovial layers are somewhat edematous and infiltrated with lymphocytes and other forms of leukocytes, including neutrophils. There are scattered small collections of lymphocytes centered around blood-vessels. In the more active cases acute inflammatory lesions involving small blood-vessels are also noted and occasionally these seem thrombosed and often a considerable amount of acidophilic hyaline fibrin or fibrin-like material is found on or within the synovial lining tissues. Sections from the articular surfaces show a layer of vascularized and chronically inflamed connective tissue (pannus) extending over the cartilage and producing dissolution and thinning of this joint element. The underlying bone is atrophic. In the patients with arthritis of long standing, microscopic studies of the joint surfaces show that they are joined together by dense fibrous tissue pannus that is moderately infiltrated diffusely and in focal areas with lymphocytes. In some patients, this connective tissue bridge is undergoing calcification and even bone formation. The patients with the Strümpell-Marie variety of rheumatoid arthritis showed fundamentally the same pathologic processes in the joints of the spine with calcification of the spinal ligaments in all our cases. The shortest duration of this disease was 7 years in our group.

Table 1 summarizes the clinical facts and the pathologic findings in the hearts of these patients.

TABLE 1.—CLINICAL DATA AND PATHOLOGIC OBSERVATIONS ON THE HEARTS OF 23 AUTOPSIED CASES OF RHEUMATOID ARTHRITIS.

No.	Sex.	Clinical diagnosis.*	Age at onset of R.A. (yrs.).	Age at death (yrs.).	History of rheumatic fever.	Age at time of R.F. (yrs.).	Age at time of cardiac diagnosis (yrs.).	Age at time of cardiac symptoms (yrs.),	Weight (gm.).	Pathologic cardiac findings at autopsy.			Cause of death.
										Valves involved.	Pericardium.	Histologic.	
1	F	R.A.*–R.H.D.*	31	53	..	..	52	Never	400	Mitr. thickening and retraction	Active adherent throughout	Healing inflammatory pericarditis	Br. pneum., pul. tuberc.
2	F	R.A.–R.H.D.	(20–25)? 45	49	..	..	40	40	485	Mitr. sten.	Healed adherent patch	Inact. rheum. myocard. and valv. changes	Mult. cbr. emboli, subac. bact. endocarditis.
3	M	R.A.–R.H.D. (Strümpell-Marie)	24	35	+	13	13	Never	360	Sl. mitr. sten., aortic sten.	Normal	Inact. rheum. myocard. and valv. changes	Cbr. hem., subac. bact. endocarditis.
4	M	R.A.–R.H.D. (Strümpell-Marie)	41	51	..	..	48	51	610	Aortic sten.	Normal	Inact. rheum. myocard. and valv. changes	Cardiac failure.
5	F	R.A.	45	69	..	..	Postmortem	Never	530	Sl. mitr. sten.	Normal	Inact. rheum. valv. changes	Br. pneum.
6	M	R.A.	34	42	..	..	Postmortem	Never	Sl. enlarged	Sl. mitr. sten.	Normal	Not reported	Cerebral thrombosis.
7	F	R.A. (Still's)	11	12	..	..	(Adhesive pericarditis) 12	12	340 (3 × normal)	None	Healing adherent throughout	No rheum. changes	Cardiac failure, acute staph. endocarditis.
8	F	R.A.	47	72	..	..	...	..	260	None	Healed adherent throughout	No rheum. changes	Br. pneum.
9	M	R.A. (Strümpell-Marie)	31	42	±	5 (chorea)	...	..	310	Art. scler. plaques, aortic mitr. pulmon.	Normal	No rheum. changes	Amyloidosis, nephritis.
10	F	R.A.	52	60	..	..	...	..	190	None	Normal	No rheum. changes	Purulent peritonitis.
11	F	R.A.	36	44	..	..	...	..	360	None	Normal	No rheum. changes	Rupt. esoph. varix, cirrhosis of liver.
12	F	R.A.	35	49	..	..	...	..	170	None	Normal	No rheum. changes	Postop. shock.
13	M	R.A.	23	35	..	..	...	..	310	None	Normal	No rheum. changes	Postop. staph. septicemia.
14	F	R.A. (Strümpell-Marie)	24	41	..	..	37 Patent ductus arteriosus	Never	300	None	Normal	No rheum. changes, patent duc. arter.	Carcinoma of breast.
15	F	R.A.	42	59	..	..	...	..	Normal	None	Normal	No rheum. changes	Volv., br. pneum.
16	M	R.A.	25	32	+	17	...	..	290	None	Normal	Not reported	Chr. glom.-nephritis.
17	M	R.A.	37	44	+	15	...	..	410	None	Normal	No rheum. changes	Erysipelas, amyloidosis
18	F	R.A.	69	76	..	..	...	..	325	None	Normal	No rheum. changes	Carcinoma of uterus.
19	M	R.A. (Strümpell-Marie)	21	31	..	..	...	..	250	None	Normal	No rheum. changes	Staph. septicemia.
20	M	R.A. (Strümpell-Marie)	51	58	..	..	...	..	300	None	Normal	No rheum. changes	Postop. fat embolus.
21	M	R.A.	25	37	..	..	...	..	330	None	Normal	No rheum. changes	Chr. nephr., br. pneum.
22	F	R.A. (Still's)	9	27	..	..	...	..	330	None	Normal	No rheum. changes	Pul. tuberc., br. pneum.
23	M	R.A.	15	23	..	..	...	..	..	..	Normal	No rheum. changes	General amyloidosis.

Gross Lesions in the Heart. Six (Cases 1 to 6) of 23 cases of rheumatoid arthritis had cardiac changes at autopsy characteristic of those usually found subsequent to rheumatic fever with cardiac involvement. Four of these 6 cases showed varying degrees of mitral stenosis and 1 had aortic stenosis. Case 3 had slight mitral stenosis and moderate aortic stenosis of 22 years' standing. The weight of the hearts of these patients varied from 360 to 610 gm. with an average weight of 477 gm.

Cases 1 and 2 also had gross pericardial involvement. Case 1 showed an active adherent pericarditis obliterating the pericardial space while Case 2 had a healed adherent patch of pericarditis.

Two additional patients (Cases 7 and 8) had adhesive non-constricting pericarditis. One (Case 7) was healing and occurred concomitantly with very active rheumatoid arthritis (Still's disease) in a 12-year-old girl; the pericardial and pleuropericardial adhesions produced cardiac hypertrophy (340 gm.) but there were no endocardial changes before or after death and multiple sections of the pericardium and myocardium showed no Aschoff nodules or other pathognomonic changes of active rheumatic fever. In the second (Case 8) the pericarditis was found to be healed and thinly fibrous in a 72-year-old woman with no history of rheumatic fever; in this case the heart weighed 260 gm., here again rheumatic stigmata were absent.

The cardiac lesions not consistent with those of rheumatic fever found in 13 of the remaining 14 cases were mild arteriosclerotic changes in the older patients and consistent with their age. In none of these were the cardiac changes lethal. The remaining patient (Case 14) had a symptomless congenital ductus arteriosus, diagnosed antemortem.

Histologic Lesions. In no case did the histologic examination disclose active or inactive rheumatic changes in the tissue which might not have been apparent at the gross examination. In only 1 of the 6 cases with gross cardiac changes did the histologic examination reveal activity of the lesions with changes that may have been due to active rheumatic fever. Case 1 had at autopsy a healing inflammatory pericarditis in the presence of active pulmonary tuberculosis and terminal bronchopneumonia. The activity of this pericarditis might have been due to the pulmonary infection or the rheumatic fever state, but neither Aschoff nodules or tubercles were found in the sections. Therefore it was not possible to conclude more than that this lesion might represent an active rheumatic fever change, but that it may be entirely dependent upon the pulmonary infection. The fact that 3 of Cases 2, 3, 4 and 5 had terminal pulmonary infection without even questionable active rheumatic fever changes in the tissues could be interpreted to favor the possibility that the active tissue changes in Case 1 might be due to rheumatic fever. In Case 5 there was healed rheumatic

mitral valve thickening with terminal platelet deposits, but no active rheumatic lesions were seen. Histologic examination revealed inactive rheumatic fever changes in the valve leaflets and myocardium in the other cases (Cases 2, 3 and 4, Table 1).

Clinical Observations and Comment. There were 12 female and 11 male patients in this series, and of the latter, 5 had a Strümpell-Marie type of involvement. Three of each sex had rheumatic changes in the heart at autopsy. Rheumatoid arthritics of the usual type had about the same frequency of cardiac changes as did the Still or Strümpell-Marie varieties.

FIG. 1.—Incidence of rheumatic heart disease at autopsy as related to the age of onset of rheumatoid arthritis.

Figure 1 reveals no tendency for the age of onset to have any effect on the incidence of cardiac changes due to rheumatic fever. The average age of onset of rheumatoid arthritis of patients without cardiac changes was 29, 3 years less than the average for those with cardiac changes, 32 years.

Of the 6 cases with rheumatic cardiac changes 3 had a rapid onset of their arthritis, 1 moderately rapid and 2 insidious.

Three patients (Cases 3, 16 and 17) gave a definite clinical history of rheumatic fever but only Case 3 had subsequent rheumatic cardiac changes demonstrable at death and these were inactive. Correcting the statistics by the exclusion of this patient, 5 of 22 patients (22%) dying with rheumatoid arthritic changes in the joints had rheumatic cardiac changes at autopsy unexplained by a known previous attack of rheumatic fever. This, while an impressive finding, is less than one-half the percentage found by Baggenstoss and Rosenberg[1] in a series of 25 cases, even when their series is corrected for the same factor.

While a series of this size does not lend itself to statistical analysis, there are three important factors which appreciably temper the importance of finding 22% with rheumatic cardiac changes at autopsy. First, in one-half of the patients in which there were rheumatic changes at autopsy the heart was the center of interest ante- and postmortem. Two died of subacute bacterial endocarditis superimposed on inactive rheumatic vulvulitis and 1 of cardiac decompensation resulting from aortic stenosis and cardiac hypertrophy. Only 3 of 19 patients (15%) dying of non-cardiac causes had rheumatic cardiac changes at autopsy. Second, 4 of this group of 23 patients (17%) had clinical signs of rheumatic heart disease antemortem. This is a significantly larger proportion than the 7% found by Dawson and Tyson[7] and the 5% found in our clinic[2] in 100 consecutive rheumatoid arthritic patients. Third, as clinical activity of the rheumatoid arthritis was usually present at the time of death, it seems unusual, if the two diseases are related, that only 1 case in 23 (4%) showed signs of active rheumatic fever and even in this one, these signs were not pathognomonic but only suggestive. These observations appear to make this group selected rather than usual, but why they should come to autopsy more than an unselected group is not clear, unless the type of fatal illness led to hospitalization and more intensive study. It is well known that sufferers of rheumatoid arthritis do not die of this disease and that many die of other causes in nursing homes or in their own homes where facilities for autopsy examination are not readily accessible.

Summary and Conclusions. Of 23 autopsied cases of rheumatoid arthritis, 6 were found to have changes in the heart valve leaflets and myocardium similar to those that usually follow rheumatic fever. The histologic lesions of 1 of these 6 could possibly be considered active and 5 were inactive in character. Excluding 1 patient because of definite rheumatic fever and rheumatic heart disease present in childhood, 22% had rheumatic cardiac lesions. The factors of accentuation on cardiac death, the relatively large group with cardiac changes antemortem as compared to control groups, and the small number of cases (possibly 1) with active rheumatic fever lesions have been pointed out. The rheumatoid arthritics in this apparently selected series have a rather high incidence of cardiac

lesions similar to those that follow rheumatoid arthritis. A coincidence, a relationship of rheumatic fever and rheumatoid arthritis or the possibility that the heart disease is related to rheumatoid arthritis might be inferred from this data. Since patients with rheumatoid arthritis have to die of some other cause than their disease, it would be safer and probably wiser, as yet, to delay a final conclusion until further studies teach us which one of the above three situations truly obtains. In the clinical treatment of these patients, we have preferred to regard the cardiac changes as a coincidence of rheumatic heart disease and rheumatoid arthritis.

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THE RÔLE OF HEART DISEASE IN THE PSYCHOSES OF THE SENIUM.

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The recent increased interest in geriatrics has stimulated considerable research in this field particularly in connection with the psychoses of the senium. Whereas formerly psychiatrists were content with descriptive studies of the clinical and histopathologic features of these conditions, attention now has turned toward inquiries into the physiologic changes involved.

The main focus of investigation at present centers upon cerebral metabolism. Cameron *et al.*[2] have suggested in psychoses of the senium that the capacity of the cerebral tissues to take up oxygen is reduced. They point out that the average arterial oxygen is definitely lower than normal (16.31 vol. %) and that arm-to-carotid circulation time is definitely lengthened (25.6 seconds). Pursuing this line of investigation further, Cameron and Rosen[1] have demonstrated that there is decreased reactivity of the intracranial vessels

in the aged as shown by a significantly diminished response to the action of histamine upon cerebrospinal fluid pressure.

The present study was undertaken from this same department to demonstrate whether circulatory insufficiency plays a significant part in contributing to the relative cerebral anoxia that obtains in these cases.

Method. The case material consisted of 43 patients suffering from psychoses associated with the senium. After psychiatric evaluation of the types of conditions involved, the cardiovascular status of each case was evaluated by careful review of medical history, physical examination, search for pertinent signs and symptoms, radiographic studies of the size of the cardiac shadow, electrocardiograms, and in doubtful instances, consultation with the Medical Service of the Albany Hospital. The classification employed was that of the New York Heart Association. The cases fell into 3 groups as follows:

1. No evidence of cardiovascular disorder (16 cases).
2. Class I heart disease, *i. e.*, organic heart disease, but capable of carrying on ordinary activities without undue fatigue, palpitation, dyspnea or chest pain (15 cases). Included in this group were 2 cases of Class IIA heart disease, *i. e.*, fully compensated but liable to develop dyspnea upon moderate exertion.
3. Class IIB and III heart disease, *i. e.*, patients with activities greatly limited manifesting signs of congestive heart failure on slight exertion (IIB) or with signs and symptoms of congestive failure while at rest (III, 12 cases). In this group the patients were obviously suffering from a toxic (cardiac) psychosis superimposed upon or aggravating the senile state.

The symptoms present in all cases were characteristic of the psychoses of the senium—loss of recent memory, confusion, disorientation, delusional and occasionally hallucinatory experiences, impaired sense of values, changes in mood and habit deterioration.

Determinations of venous pressure and arm-to-carotid circulation time were made. The venous pressures were obtained by a modification of the direct method of Taylor *et al.*[11] An L-shaped calibrated tube about 30 cm. in length and 3 mm. in bore is attached by an adapter to a 3-way stopcock which supports a 10-cc. syringe and a 20-gauge needle so that both syringe and needle lie in a straight line. The apparatus is autoclaved and the syringe partially filled with physiologic saline with which the manometer in turn is filled to within a few centimeters of the top. The patient* is in the recumbent position with the upper extremity supported by pillows so that an antecubital vein is 5 cm. below the angle of Luis, thus approximating the blood level in the right auricle. The horizontal arm of the manometer is adjusted to this same level (it was found that when this was done, minor changes in the position of the arm did not affect the venous pressure level because, once the needle is in the vein, a closed system exists between the manometer arm and the heart). The stopcock is then set so that venipuncture can be done. A sufficient interval is taken to allow for compression cuff venous stasis to subside. Some of the saline remaining in the syringe is then used to wash the withdrawn blood back through the needle into the vein and the manometer is switched in. The saline level in the manometer then drops to the level indicating the venous pressure and is read off on the calibrated tube in centimeters of physiologic saline. The stopcock is turned again and blood withdrawn into the syringe to test for possible clotting.

* All determinations made under basal conditions, *i. e.*, in the morning before patient has arisen from his bed or has breakfasted.

The manometer is refilled with saline and the venous pressure rechecked. The readings should not vary by more than 1 cm. The upper limit of normal is accepted as 10 cm.

Arm-to-carotid circulation time was determined by the cyanide method of Robb and Weiss[10] with normal values ranging from their value of 15.6 seconds to 18.7 seconds reported by Freeman.[4]

Tests were repeated at least once on different days.

Results. (See Table 1.) The averages presented show definitely abnormal findings in the Class IIB–III group, whereas the other two groups reveal practically similar values, namely, venous pressures within the normal range, and circulation times significantly elevated but markedly lower than the average in the Class IIB–III group.

TABLE 1.—VENOUS PRESSURE.

Case No.	Without organic heart disease.			With minimal organic heart disease.			With Class II B–III heart disease.		
	Age.	Ven. pres.	Circ. time.	Age.	Ven. pres.	Circ. time.	Age.	Ven. pres.	Circ. time.
1	60	6.0*	28.0†	64	9.3*	22.6†	68	15.5*	45.6†
2	68	5.5	26.0	69	8.0	33.6	55	8.5	24.0
3	68	8.8	24.0	67	8.8	29.8	77	8.9	28.1
4	74	6.3	27.5	79	8.8	27.0	71	5.6	26.0
5	75	7.5	24.7	76	8.5	23.2	59	15.2	27.6
6	73	6.8	24.6	60	8.6	13.5	74	12.0	15.2‡
7	67	..	18.5	80	6.3	25.6	82	12.0	31.6
8	57	4.1	20.5	87	3.0	20.5	70	13.5	29.0
9	77	10.0‡	25.0	70	9.5	26.5	65	15.5	22.4
10	85	6.8	17.5	71	8.8	19.6	74	10.5	39.7
11	65	6.5	19.0	73	7.3	17.2	73	6.8	38.0
12	63	14.5‡	16.0	71	10.2‡	20.5	71	11.0	25.4
13	66	6.5	16.0	70	3.6	18.6			
14	65	7.2	27.0	73	8.0	20.0			
15	60	7.2	21.0	77	16.0‡	19.6			
				70	5.8	27.8			
Average	72.3	8.1	22.5	68.2	7.4	22.3	69.9	11.2	29.3

* = Venous pressure in centimeters of physiologic saline.
† = Circulation time in seconds.
‡ = Patient markedly agitated and tense.

Discussion. Fishberg *et al.*[3] and other investigators have stated that venous pressure is normal in pure left heart failure when the right ventricle is adequately functioning but is increased in right heart failure. Hitzig *et al.*[7] and other workers have proven that in left heart failure arm-to-tongue circulation time (gluside method) is elevated while arm-to-lung circulation time (ether method)[6] is within normal limits. The results of venous pressure and circulation time tests are therefore highly significant in determining the presence of cardiovascular disorder aside from other laboratory and clinical methods.

The abnormal values found in the Class IIB–III group confirm the status of these cases as decompensated cardiacs with right or/and left heart failure in whom the psychosis is due to a relatively marked degree of cerebral anoxia occurring during the senium. However, the similarity in the findings in the other two groups, one with minimal organic, non-symptomatic heart disease, and the other without

demonstrable organic heart disease suggests that cardiac disorder plays no significant rôle in the large group of the psychoses of the senium except as may be indicated by the moderate elevation of the circulation time. This latter may be nothing more than a mild circulatory slowing consistent with the generally decreased metabolism attending senescence, as indicated by Kise and Ochi[8] and Lewis.[9] Other conditions not associated with demonstrable cardiovascular disorder may have an increased circulation time as shown by Freeman[4] in a comparative study of normal and schizophrenic subjects. However, whether or not a mild degree of subclinical arteriosclerosis may be responsible for this increase cannot be definitely ruled out. Gottlieb[5] found a mean circulation time of 24.4 seconds for 11 patients with slight arteriosclerosis. Wortis *et al.*[12] studied a group of cerebral arteriosclerotics ranging from 59 to 97 years of age and found that the circulation time was somewhat slow concluding that there is reduced brain metabolism. One must question the comparability of their findings, however, since they regard an average of 16.6 seconds as abnormal compared to their normal of 15 seconds obtained by a method which probably did not utilize basal conditions.

Summary and Conclusions. 1. The cardiovascular status of 43 cases of psychoses in the senium was carefully evaluated.

2. Venous pressure and arm-to-carotid circulation times were determined.

3. Twelve cases had advanced cardiac disease and showed markedly abnormal values, 15 cases had minimal organic heart disease without symptomatology; and 16 had no demonstrable organic heart disease. These last 2 groups had normal venous pressures and very moderately elevated arm-to-carotid circulation times.

4. The significance of the above findings is considered and the rôle of arteriosclerosis discussed as a possible cause for the moderately elevated circulation time.

5. It is concluded that cardiac disease plays a minor rôle, if any, in the psychoses of the senium in which obvious advanced heart disease is not present.

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EXTREME TACHYCARDIA: WITH REPORT OF NON-FATAL PAROXYSMS FOLLOWING MYOCARDIAL INFARCTION.

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In 1921 Lewis[12] and his associates showed that when the auricles of a mammalian heart were stimulated faster than 300 per minute, the auriculo-ventricular node failed to transmit each stimulus and as a result dropped beats, a 2:1 rhythm occurring with consequent slowing of the ventricles. The critical rate at which 2:1 rhythm occurs in the auricular muscle was found by Lewis to be approximately 450; the critical rate for the A–V node 270–300 per minute; the critical rate for the ventricle was intermediate. Lewis also found that if the auricles were driven at rates surpassing 300 per minute, the ventricles would beat at a lower rate. However, it was not the ventricles which failed to respond, for it responded if the stimulus was directly applied to it, but the A–V node which failed to transmit. In the mammalian heart, therefore, the upper limit of ventricular rate to be expected in extreme tachycardia arising in the auricles or A–V node should be in the neighborhood of 300 beats per minute.

A review of the literature shows that the upper limit at which the ventricles of the adult human heart can beat for a relatively prolonged period is approximately 300 per minute, although in infancy several cases with a higher rate have been recorded. Fifteen cases with a recorded ventricular rate of 300 or more per minute have been reported in the literature.[3–8,10,14–18]

To this group we wish to add 2 cases. The first was one of acute coronary occlusion in which paroxysmal tachycardia with an extremely rapid rate occurred twice—once for a period of 12 hours with a ventricular rate of 310 per minute, and, after an interval of a day and a half, for a period of 34½ hours, with a ventricular rate of 303 per minute. Following the paroxysms, the rhythm returned to normal sinus rhythm and the patient made an uneventful recovery. The second patient was an infant, aged 22 days, who expired 2 days after the tachycardia was diagnosed.

Case Reports. Case 1. R. G., a white woman, aged 46, was admitted to Mt. Sinai Hospital, Philadelphia, to the service of Dr. A. I. Rubenstone, on June 1, 1939. She had been in comparatively good health until May 28 when she was suddenly seized with substernal pain radiating to the left shoulder and down the left arm to the finger tips and associated with dyspnea. This attack lasted about ½ hour but similar attacks recurred at intervals of about 10 minutes. The pain was evidently not very severe inasmuch as a physician was not called. Attacks occurred during the entire day of May 29. She was relatively free of attacks on the 30th but on

May 31 the recurrence of the attacks forced her to consult a physician. The medication prescribed by him gave no relief and therefore hospitalization was advised.

She had suffered from gastro-intestinal symptoms for many years and had been aware of an elevated blood pressure but otherwise her past medical history was unimportant. Her menses had been irregular for 2 years and there had been mild menopausal symptoms.

Examination on admission revealed a very obese woman (weight 241 pounds, height 60 inches) who appeared to be in great pain. There was slight cyanosis of the lips. Percussion of the cardiac borders was difficult because of marked obesity. The heart action was regular, the sounds were distant but no murmurs were heard. The blood pressure was 96/60, but the following day was 170/110 and then dropped again to 94/60. Examination was otherwise negative except for diseased tonsils. The temperature on admission was 99° F. but rose to 101° at 8 P.M. Blood count showed 96% Hb. (13.9 gm.), 4,820,000 R.B.C. and 12,900 W.B.C. of which 68% were polymorphonuclear cells. The urine was essentially negative. The sedimentation time was 25 mm. in 60 minutes. Roentgen ray of the chest on 6–2–39 disclosed a marked enlargement of the heart and a wide supracardiac area, but the lungs were essentially negative. Electrocardiogram taken on 6–2–39 (Fig. 1, *A*) showed in the chest lead the typical pattern of an acute infarction involving the anterior surface of the left ventricle, but the limb leads failed to show the usual pattern of an infarction until 6–14–39 (Fig. 1, *B*). During this interval the patient was comfortable but the temperature was irregular and the sedimentation rate was rapid (27 mm.). On 6–22–39 the patient was awakened by severe palpitation and soon became cold and clammy. Her blood pressure was 100/80. An electrocardiogram showed extreme tachycardia of 310 per minute (Fig. 2, *A*). She was placed in an oxygen tent, given morphine ($\frac{1}{4}$ gr.) to allay restlessness and small doses (3 gr.) of quinidine sulphate every 4 hours. The attack lasted approximately 12 hours and the electrocardiogram taken at the end of that time showed normal sinus rhythm. Quinidine was continued and the patient was comfortable until 8 A.M. of 6–24–39, when palpitation recurred. An electrocardiogram (Fig. 2, *B*) showed extreme tachycardia with a rate of 303 per minute. She was again placed in an oxygen tent, opiates given for restlessness and quinidine was given in 10 gr. doses, 40 grains being given in 18 hours. In addition, powdered digitalis, $1\frac{1}{2}$ gr. t.i.d., was given. However, the attack continued and on the morning of 6–25–39, the patient appeared moribund. The blood pressure was 80/68. Nine grains of digitalis were given intramuscularly at 11 A.M. and repeated at 5 P.M. An electrocardiogram taken at 5 P.M. showed no change. At 6.30 P.M. she was examined and there was no change in rhythm. A short time later the paroxysm ceased, having lasted at least $34\frac{1}{2}$ hours. Thereafter her stay in the hospital was uneventful although her temperature continued to be slightly elevated. Her blood pressure rose and varied from 132/80 to 140/85. She was discharged from the hospital on 7–19–39. Since discharge she has been in good condition and has not experienced any attacks of cardiac pain or palpitation. Figure 1, *C* is the electrocardiogram taken 12–2–40.

CASE 2. T. H., a white male infant, was born of healthy parents on 5–7–42. He was examined immediately after birth and again on 5–17–42 and was thought to be normal. The child was apparently in good health until the night of 5–28–42 when his mother noticed slight pallor, which was more definite on 5–29–42. At this time the maid thought the heart rate was very rapid; the mother volunteered the statement that for the preceding 4 or 5 days the heart appeared to be fast when she held the baby over her shoulder but considered it normal. On the evening of 5–29–42, the

TABLE 1.—DATA OF 17 CASES OF EXTREME TACHYCARDIA.

	Author.	Age.	Sex.	Color.	Diagnosis of arrhythmia.	Paroxysms.			Signs and symptoms during attack.	Other cardiac abnormalities.	Associated conditions.	Outcome.*	Effect of treatment.	Record
						Number.	Longest.	Record vent. rate, per mm.						
1	McKenzie, 1911	47 yrs.	M	W	Par. tachy.	Numerous	30–60 min.	290–300	Livid; very weak in attacks	None	None	R	None during extreme tachy.; later flutter; dig. produced fibrillation, then normal rhythm	Polygram
2	Blackford and Willius, 1918	32 yrs.	F	W	Aur. flutter	Repeated	2 hrs.	300	Severe palpitation	None	Exophth. goiter	R	Dig. produced fibrillation but flutter returned on withdrawal; cured by thyroidec.	E.C.G.
3	Werley, 1925	4 days	M	W	Par. tachy.	Probably 2	At least 2 hrs.	307	Very cyanosed; liver enlarged to umbilicus; pul. edema, p.m.	Widely patent foramen ovale	No def. diag.; fever, vomit.	D	Not stated	Polygram
4	Russell and Ellison, 1927	3 mos.	F	W	Supravent. tachy.	Probably many	5 days	300	Complete flac.; child believed dead; unconscious; later marked cyanosis and restless.	Cong. heart dis.; enlarged to right	None	R	Quinidine given; doubtful effect	Polygram
5	Langley, 1928	14 yrs.	M	W	Supranodal par. tachy.	?	?	300	None	Enlarged (?) left aur. on Roentgen ray; clinically negative	None	R	Not stated	E.C.G.
6	Bunn, 1933	50 yrs.	M	W	Vent. tachy.	1	5 hrs.	300	Collapse; cold and clammy; marked drop in bl. pr. (60/40); pul. edema near end of paroxysm	None	Exophth. goiter	R	Quinine hydrochloride, 7 gr. ss. intraven. produced fibrillation; normal sinus rhythm 48 hrs.	E.C.G.
7	Farr and Wegman, 1935	24 days	M	W	Extreme tachy.	6	At least 8 hrs.	300	Sl. cyanosis; dyspnea; liver 5 cm. below costal margin; roentgenogram showed passive congestion	None	None	R	Digitalis; no apparent favorable action	E.C.G.
8	Soeter, 1936	4 mos.	..	..	Infranodal par. tachy.	1	2 days ?	300	Apathetic, cyanotic, enlarged liver, vomiting and labored resp.	None	Marked vag. discharge; 20,300 W.B.C.	R	Ouabain and quinidine	E.C.G.
9	Soeter, 1936	3 mos.	..	..	Infranodal par. tachy.	1	2 days ?	300	Apathetic, cyanotic, enlarged liver, vomiting and labored resp.	None	Marked vag. discharge; 20,300 W.B.C.	D	Not stated	E.C.G.
10	Soeter, 1936	3 mos.	..	..	Infranodal par. tachy.	1	2 days ?	300	Apathetic, cyanotic, enlarged liver, vomiting and labored resp.	None	Marked vag. discharge; 20,300 W.B.C.	R	Ouabain and quinidine	E.C.G.
11	Soeter, 1936	3 mos.	..	..	Infranodal par. tachy.	1	2 days ?	300	Apathetic, cyanotic, enlarged liver, vomiting and labored resp.	None	Marked vag. discharge; 20,300 W.B.C.	R	Ouabain and quinidine	E.C.G.
12	Soeter, 1936	3 mos.	..	..	Infranodal par. tachy.	1	2 days ?	300	Apathetic, cyanotic, enlarged liver, vomiting and labored resp.	None	Marked vag. discharge; 20,300 W.B.C.	R	Ouabain and quinidine	E.C.G.
13	Soeter, 1936	3 mos.	..	..	Infranodal par. tachy.	1	2 days ?	300	Apathetic, cyanotic, enlarged liver, vomiting and labored resp.	None	Marked vag. discharge; 20,300 W.B.C.	R	Ouabain and quinidine	E.C.G.
14	Soeter, 1936	3 mos.	..	..	Infranodal par. tachy.	1	2 days ?	300	Apathetic, cyanotic, enlarged liver, vomiting and labored resp.	None	Marked vag. discharge; 20,300 W.B.C.	R	Ouabain and quinidine	E.C.G.
15	Soeter, 1936	3 mos.	..	..	Infranodal par. tachy.	1	2 days ?	300	Apathetic, cyanotic, enlarged liver, vomiting and labored resp.	None	Marked vag. discharge; 20,300 W.B.C.	R	Ouabain and quinidine	E.C.G.
16	Soeter, 1936	3 mos.	..	..	Infranodal par. tachy.	1	2 days ?	300	Apathetic, cyanotic, enlarged liver, vomiting and labored resp.	None	Marked vag. discharge; 20,300 W.B.C.	R	Ouabain and quinidine	E.C.G.
17	Soeter, 1936	3 mos.	..	..	Infranodal par. tachy.	1	2 days ?	300	Apathetic, cyanotic, enlarged liver, vomiting and labored resp.	None	Marked vag. discharge; 20,300 W.B.C.	R	Ouabain and quinidine	E.C.G.

								tal margin; roentgenogram showed passive congestion				favorable action	
8	Soeter, 1936	4 mos.	..	..	Infranodal par. tachy.	1	2 days ?	300	Apathetic, cyanotic, enlarged liver, vomiting and labored resp.	None	Marked vag. discharge; 20,300 W.B.C.	R	Ouabain and quinidine	E.C.G.
9	Lyon, 1937	31 days	F	B	Aur. flutter	Several	10 hrs.	310–313	Dyspnea; liver enlarged	None	Strept. mening.	D	Not stated	E.C.G.
10	Campbell, 1937	1 mo.	M	W	Nodal par. tachy.	2	Indefinite, sev. days?	300	Dyspnea; enlarged liver	None	?	R	Dig. 2 minims t.i.d.; 1 attack stopped suddenly after 4 doses; another on 3d day	E.C.G.
11	Puglisi, 1939	10 days	F	W	Nodal par. tachy.	Probably many	?	345	Marked cyanosis and dyspnea; salivation	Roentgenogram showed enlarg. to right ? cong. heart disease	None	D	Quinidine and coramine; no effect; carotid sinus pr.; reduced rate to 285	E.C G.
12	Berry, 1940	16 mos.	F	W	Par. tachy.	2	About 4 days	336–340	Marked pallor	None; roentgenogram showed enlarged ht. shadow during attack	G.I. upset	R	Not stated	E.C.G.
f13	Hubbard, 1941	1 mo.	F	..	Aur. par. tachy.	1	38 hrs.	300	Vomiting; pallor	Cong. heart disease?	Pul. infection	R	Attack stopped spon.	E.C.G.
14	Hubbard, 1941	2 wks.	F	..	Supravent. par tachy.	2	4 days	300	Vomiting; pallor; rapid resp.; mod. enlarged liver	Roentgenogram showed mod. enlarged ht.	Xanthochromic spinal fluid	R	Digitalis, stopped attack after .1 gm. in 1 dose	E.C.G.
15	Hubbard, 1941	7 mos.	M	..	Aur. par. tachy.	1	?	305	Labored breathing	None	Pneumonia	R	Digitalis, stopped attack after .3 gm. in 1 day	E.C.G.
16	Edeiken, 1942	46 yrs.	F	W	Supravent. par. tachy.	2	34½ hrs.	310	Marked pallor; apprehension and distress; marked drop in bl. pr.	Acute infarct. of ant. surf. of left vent.; marked card. enlargement; aort. sclerosis; mod. hypertension	Menopause obesity	R	Quinidine, 1st paroxysm; digitalis, 2d paroxysm; questionable effect	E.C.G.
17	Edeiken 1942	22 days	M	W	Supravent. par. tachy.	1	At least 2 days	320	Pallor. cyanosis; enlarged liver; resp. distress	None	?	D	Oxygen and symptomatic treatment	E C.G.

* R = Recovered. D = Died.

child was examined by Dr. Elizabeth K. Rose and because of the extreme tachycardia was immediately admitted to the hospital of the University of Pennsylvania, service of Dr. Joseph Stokes. On examination the child appeared somewhat pale but was not cyanotic, the respirations were rapid and shallow but otherwise the infant did not appear to be in distress. The heart did not appear enlarged to percussion, the heart action was regular but extremely rapid, ±320 per minute; no murmurs were heard. During examination the heart rate suddenly dropped to 160 per minute but 4 minutes later again doubled to 320 per minute. The lungs were clear but the liver was palpable 2 cm. below the right costa lmargin; the limbs were negative. An electrocardiogram made 5–30–42 (Fig. 2, *C*) disclosed a tachycardia of supraventricular origin of 320 per minute. A roentgenogram of the chest on 5–30–42 disclosed possible widening of the base of the heart; the lung fields were clear. On the evening of 5–30–42 there was slight cyanosis, the chest was clear, but the liver appeared to have enlarged. At 12.30 A.M. 5–31–42, the child suddenly awoke from sleep with a shrill cry and at this time cyanosis was more marked, respirations rapid and labored and the temperature subnormal. The child was placed in an oxygen tent but did not rally and expired on 6–1–42 at 3.15 P.M.

Postmortem examination (1½ hours after death) failed to reveal the cause of death; except for slight dilatation of both ventricles the heart was normal. The widened mediastinal shadow corresponded to the right lobe of the thymus. The thymus was top normal in size, 20 gm., but was not in a position to exert pressure on the heart or mediastinal structures.

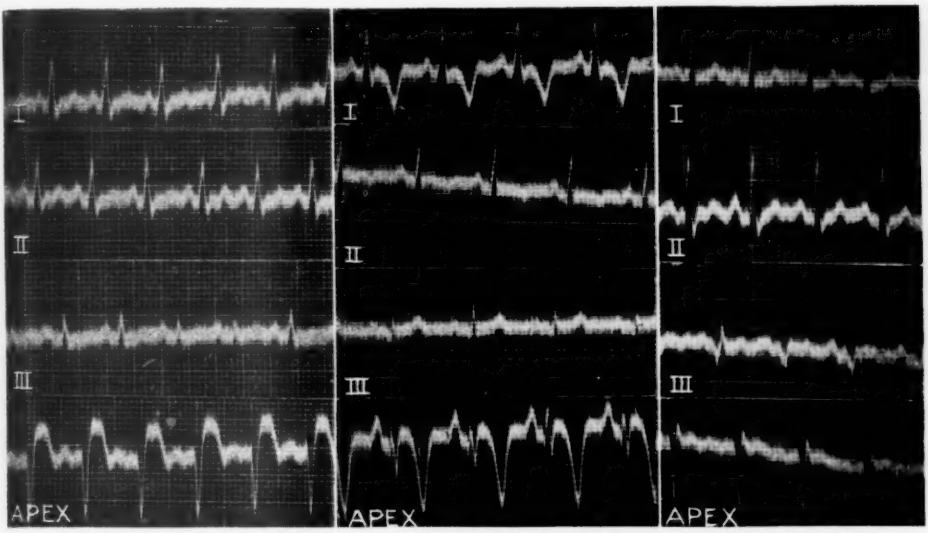
Discussion. Data pertinent to the 17 cases with a recorded ventricular rate of 300 or more per minute are presented in Table 1. Certain results of the analysis of this material seem to merit discussion.

Age. The youngest patient in this series was 4 days old, the oldest 50 years. Twelve of the group were infants, others were 14, 32, 46, 47 and 50 years of age. Not only has the majority of cases occurred in infants but the fastest recorded rates and the longest paroxysms have also been found in infants. These observations would seem to bear out the statement frequently made that there is a greater responsiveness of the conduction system and greater elasticity of the musculature in hearts of very young children, thus enabling them to tolerate prolonged attacks of rapid heart action and make a rapid and apparently complete recovery.

Status of the Heart. Of the 4 instances (Cases 3, 9, 11 and 17) in which death occurred (all infants) postmortem examination was permitted in 3 (3, 9 and 17) and in each case a normal myocardium was found; in Case 3 there was a widely patent foramen ovale and in Case 9 death was due to streptococcic meningitis. The cause of death in Cases 11 and 17 was not definitely determined but a congenital heart lesion was believed to have been present in Case 11. Another (Case 4) of the infant group had congenital heart disease and congenital heart disease was suspected in Case 13, but the remaining 6 (Cases 7, 8, 10, 12, 14 and 15) disclosed no clinical evidence of heart disease. In Case 12 Roentgen ray examination during an attack showed an enlargement of heart shadow, but this cannot be considered significant inasmuch as similar findings have

been observed by Keith and Brown,[9] and Levine and Golden[11] in cases of paroxysmal tachycardia with subsequent return of the heart to normal size. In 8 of the 12 cases in the infant group, therefore, the heart was considered normal.

In the boy of 14 (Case 5) a roentgenogram disclosed a questionable enlargement of the left auricle, but on clinical examination the heart was found normal. Two cases (2 and 6) in the adult group, aged 32 and 50, had exophthalmic goiter, the tachycardia following operation in 1. In both instances, however, subsequent examinations revealed normal hearts. Our case (16) had an acute myocardial infarction.



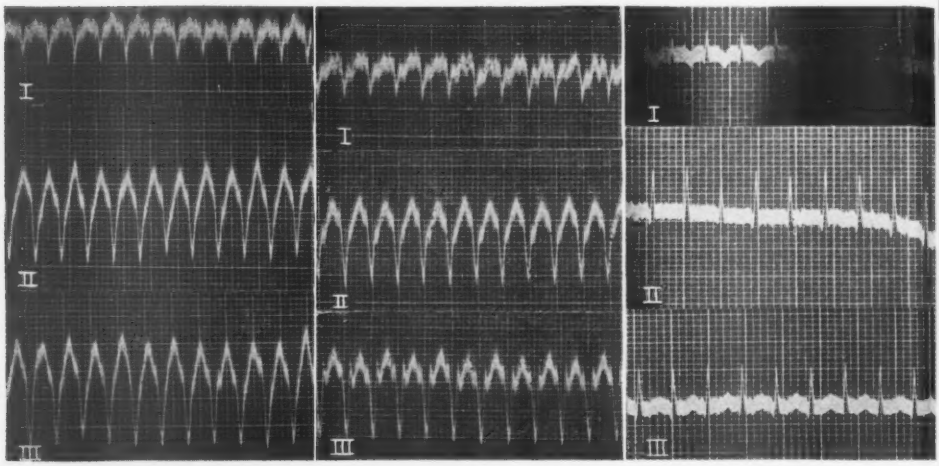
A *B* *C*

FIG. 1.—Case 1. *A*, Record taken 6-2-39, 2 days after attack of severe chest pain. Ventricular rate ca 150 per minute. *B*, Record taken 6-14-39, 2 weeks after the onset of pain and 8 days before the first paroxysm of extreme tachycardia. Rate 100. *C*, Record taken 12-2-40, 18 months after the attack of coronary occlusion. Rate 136.

In the majority of instances, therefore, extreme tachycardia occurred in apparently normal hearts. In only 5 of the 17 cases was there evidence of organic heart disease and in only 1 of these was there definite evidence of myocardial damage.

Associated Diseases. In 1 case (9), as stated above, streptococcic meningitis was present, 2 cases in the adult group suffered from exophthalmic goiter, in 2 cases (3 and 12) attacks seemed to be associated with a gastro-intestinal upset, and in 2 cases (13 and 15) there were pulmonary infections.

Number and Duration of Paroxysms. Both the number and duration of the paroxysms varied greatly. In 5 cases (6, 8, 13, 15 and 17) there was a single paroxysm. The number of attacks in Langley's patient is not stated, but in the remaining cases the paroxysm was repeated at least once and in some instances there were numerous attacks. The duration varied from ½ hour in Mackenzie's case (1) to 5 days in Russell and Ellison's case (4). In the adult group the attacks were usually of short duration. Those of 12 and 34½ hours observed in our cases were much longer in duration than any previously reported in an adult. The duration of the attack in Langley's patient (5) a boy of 14, was not stated. Several paroxysms in the infant group apparently lasted a number of days.



A *B* *C*

FIG. 2.—Case 1. *A*, Record taken 6-22-40, 4 hours after the onset of first paroxysm of extreme tachycardia. Rate 310 per minute; the duration of the paroxysm was 12 hours. *B*, Case 1, 2 hours after the onset of second paroxysm on 6-24-39. Rate 303; the duration of the paroxysm was approximately 34½ hours. *C*, Case 2. Record taken 5-30-42. Rate 320. Except for a period of 4 minutes during which the pulse rate dropped to 160, extreme tachycardia persisted from 5-29-42 until death of infant on 6-1-42.

Origin of the Paroxysm. The determination of the origin of the tachycardia was not ascertained with any degree of certainty except in the case (2) of 1:1 rhythm occurring during established flutter, but in only 1 case (6) was the tachycardia believed to be of ventricular origin. An examination of the electrocardiograms in our cases suggests that the paroxysms were of supraventricular origin but does not permit a distinction between auricular flutter with 1:1 rhythm and auricular tachycardia, although the halving of the ventricular rate during clinical examination of Case 17 is suggestive

of auricular flutter. Bedell[2] has suggested the term paroxysmal auricular tachysystole for cases of extreme tachycardia in which this distinction cannot be made, but we see no advantage in the adoption of such a term unless a need for its use to designate a hitherto unrecognized form of extremely rapid auricular beating can be demonstrated.

Symptomatology. Symptoms manifested during the attacks varied greatly in both the adult and infant group. Langley's patient (5) a boy of 14 had no symptoms, and Blackford and Willius' patient (2), a woman of 32 with exophthalmic goiter, walked several blocks to the office and during the first hour was not sufficiently inconvenienced to make any complaint. The patient reported by Berry (12), an infant of 16 months, had a tachycardia of 336–340 per minute which persisted for 4 days without marked symptoms. On the other hand, in Bunn's[6] and in Russell and Ellison's case (4), a child of 15 months, there was complete collapse and the child was at first believed dead.

In the remaining cases, signs and symptoms usually were not marked and of these, cyanosis or pallor, dyspnea, drop in blood pressure, congestive failure, weakness and restlessness were most prominent. Loss of consciousness occurred in only 1 case (4). Pain was not an outstanding symptom in any of the cases.

Effect of Treatment. An analysis of the cases suggests that treatment was of definite value in only 6 cases; in the remainder the attacks apparently stopped spontaneously. In Mackenzie's case (1) the patient finally developed flutter and under digitalis therapy normal rhythm was restored after the flutter was converted into fibrillation. In Bunn's case (6) regarded as ventricular tachycardia, quinine hydrochloride, 7½ gr. intravenously, produced auricular fibrillation with a ventricular rate of 150 and within 48 hours normal rhythm was restored. Cases 10, 14, and 15 were apparently favorably influenced by digitalis and Case 8 by Ouabain and quinidine. In our case, the first attack stopped after about 12 hours on quinidine therapy but the second and more prolonged one came on while the patient continued to take quinidine. Moreover, quinidine in large doses failed to stop the second paroxysm which finally ceased after large doses of digitalis. It is therefore questionable whether either quinidine or digitalis exerted any beneficial effect.

Outcome. On the basis of cases reported in the literature, Lyons stated that the prognosis in excessively rapid heart rates is good unless an associated condition is present which cannot be controlled and that excessively rapid rates occur in patients with relatively sound hearts. In Arenberg's[1] group of 39 cases of 1:1 flutter with ventricular rates of 222–300, only 1 death was attributed to the tachycardia and this was caused by a coronary occlusion due to an

antemortem clot from the left auricle. However, so far as we can determine, in no previously reported case has there been recorded an extreme tachycardia during the early stages of coronary occlusion. Although our patient recovered, it is obvious that this does not warrant a favorable prognosis in similar cases. The cause of death in 3 of the infant groups (Cases 3, 11, 17) was not ascertained and in these the possibility that extreme tachycardia may have been a major factor cannot be dismissed.

Summary and Conclusions. 1. Two cases of extreme tachycardia are added to the 15 cases previously reported with a recorded ventricular rate of 300 or more per minute; in 1 instance the tachycardia occurred during the acute stage of myocardial infarction.

2. So far as we can determine, our Case 1 is the only case in which such extreme tachycardia was recorded in the presence of acute myocardial infarction; in the other cases of extreme tachycardia the myocardium was regarded as sound.

3. Two paroxysms of extreme tachycardia occurred in the patient suffering from myocardial infarction—one lasting 12 hours with a ventricular rate of 310 per minute and another lasting 34½ hours with a ventricular rate of 303 per minute. The onset and offset in both attacks were sudden.

4. The ventricular rate of 310 per minute is the fastest sustained tachycardia recorded in the adult human heart; more rapid rates have been recorded in infants.

5. In 9 of the 15 previously reported cases, treatment did not appear to influence the paroxysms or prevent their recurrence. It is questionable whether treatment (quinidine and digitalis) exerted any beneficial effect in stopping the paroxysms complicating acute myocardial infarction.

The author wishes to express his thanks to Dr. A. I. Rubenstone and to Drs. Elizabeth K. Rose and Joseph Stokes, Jr., for permission to report the above cases.

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THE FAMILY HISTORY IN ARTERIAL HYPERTENSION

A Study of 4376 Insurance Examinations

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The concept of a hereditary factor in essential hypertension has not been accepted by all investigators. Striking reports[2,10] have frequently appeared of single families with a high incidence of hypertensive vascular disease. Nevertheless, statistical studies have not demonstrated convincingly that heredity is a major factor in the development of hypertension. In some papers, the criteria used to classify the family history have not been clearly defined. The care with which the family history is recorded and the age of the subjects are important variables which must be considered. Unfortunately, these factors have not always been taken into account. This paper covers the results of a controlled study of 4376 life insurance examinations in which only a slight relationship between the family history and the blood pressure was observed.

More than 25 years ago, Janeway[4] said that his "figures suggest a subordinate and accessory influence of inheritance for the majority of patients who have hypertension." In 1923 Weitz[9] reported a higher incidence of heart disease, edema, and apoplexy among parents of hypertensive patients than there was among parents of persons who did not have hypertension. O'Hare, Walker, and Vickers[6] compared family histories of 300 hypertensive patients whose average age was 52, with records of 436 non-hypertensive patients whose average age was 36. A family history of apoplexy, heart disease, nephritis, arteriosclerosis, or diabetes was elicited in 68% of the hypertensive group and 37.6% of the controls. Nuzum and Elliot[5] observed a positive family history in 30.8% of 500 patients with high blood pressure and 29.6% of 250 persons with normal blood pressure. The average age of their two groups was the same. Palmer[7] reported on the incidence of familial vascular disease in 100 unselected patients with hypertension and 100 controls. The difference was so slight as to have no statistical significance. Ayman[1] observed that high blood pressure was more common in the offspring of hypertensive parents than it was in children whose parents had normal blood pressure. Hines[3] noted a positive family history of hypertensive cardiovascular disease in 87% of 267 patients with essential hypertension and in 30% of 608 persons with normal blood pressure. The comparative ages were not stated. In a relatively small series, Thacker[8] elicited a family history of

hypertensive cardiovascular disease in 54% of 96 hypertensive university students and in 3% of 128 students who had normal blood pressure.

Material. The 4376 persons studied consisted of all the applicants (2188) who were refused insurance by the Northwestern Mutual Life Insurance Company in 1940 and 1941 because of high blood pressure and a control series of 2188 applicants who were issued insurance in 1940 and 1941 and whose blood pressure was normal. The control group was selected at random except that age and sex were matched with the age and sex of the applicants who had high blood pressure. The subjects were all members of the white race, and, in general, they were in moderate or good economic circumstances. It cannot be said that 4376 different families were covered because certain unavoidable duplication occurred. For example, a brother and sister might have applied for insurance and, hence, the family history would be the same. Random sampling of 1062 applications showed that each of two family histories were counted twice because two pairs of brothers were involved. Therefore, the amount of duplication was negligible. In each group there were 229 (10.5%) females and 1959 (89.5%) males. The ratio of females to males was about the same as the ratio among all applicants of similar age. The average age was about 43 years, and the age distribution was as follows:

	Distribution of cases.
Ages 10–19	55
20–29	342
30–39	389
40–49	730
50–59	553
60–65	119
	2188

Of the applicants who had high blood pressure, 83% showed an initial reading of 150 mm., systolic and/or 90 mm., diastolic, or more. Of the control group, 75% had an initial blood pressure under 140 mm., systolic, *and* 85 mm., diastolic. The examinations were made by many different examiners, most of whom would be classified as general practitioners. Every State was represented, except South Carolina, Florida, Alabama, Mississippi, Louisiana, and Texas. The examination blank is so devised that the family history is secured before the examination is made. Space is provided for recording the state of health, if living, or the cause of death, if dead, of each relative. In addition, there are specific questions regarding diabetes, apoplexy, heart disease, and kidney disease. Since the examiner does not usually take the blood pressure until the history has been recorded, disproportionately intensive questioning of hypertensive applicants is avoided.

Results. *Family History of Cardiovascular-renal Disease.* In classifying the family histories, only the parents and siblings of

the applicant were considered. The definite statement that one or more relatives, past the age of 40, had died or was ill due to heart disease, arteriosclerosis, apoplexy, Bright's disease, or high blood pressure, was accepted as evidence of familial cardiovascular-renal disease. The same criteria of classification were applied to the subjects with normal blood pressure and to those with high blood pressure. Table 1 shows that there was only a slight difference in the incidence of familial cardiovascular-renal disease. Six hundred and fifty (29.7%) of the subjects with normal blood pressure and 717 (32.7%) of those with high blood pressure had such a family history.

Family History of Hypertensive Cardiovascular Disease. In an attempt to determine the familial incidence of *hypertensive* cardiovascular disease, another classification of the family history was made. The only illnesses that were regarded as due to hypertensive cardiovascular disease were those in which the relative suffered from high blood pressure or some illness which seemed likely to be the result of hypertension. Death or illness caused by cardiac or cerebral accidents occurring between the ages of 40 and 70 was regarded as probably due to hypertension. Table 1 shows that 274 (12.5%) of the applicants with normal blood pressure had one or more instances of hypertensive cardiovascular disease among parents and siblings. Three hundred and thirty (15.1%) of the hypertensive subjects had similar histories. Again, the difference in the incidence of positive family histories is slight.

TABLE 1.—RELATION OF FAMILY HISTORY TO BLOOD PRESSURE

	2188 subjects with normal blood pressure		2188 subjects with high blood pressure	
History of parents and siblings	No.	%	No.	%
One or more cases of cardiovascular-renal disease	650	29.71 ± .98	717	32.77 ± 1.01
One or more cases of *hypertensive* cardiovascular disease	274	12.52 ± .71	330	15.08 ± 0.77
One or more cases of diabetes	66	3.01 ± .36	82	3.75 ± 0.40

The standard error (or standard deviation) of a percentage is calculated according to the formula: $SE = \sqrt{pq/n}$, where p is the per cent of the sample with the characteristic studied and q is the per cent without the characteristic. The n is the number of observations. The standard error of a difference between two percentages is equal to $\sqrt{(SE_1)^2 + (SE_2)^2}$.

The standard error of the difference between 29.71 ± .98% and 32.77 ± 1.01% is 1.41%. The actual difference (3.06%) is 2.17 times the standard error of the difference. Such a difference in one direction could occur 15 times in 1000 as a matter of chance and, therefore, the difference is probably statistically significant.

The standard error of the difference between 12.52 ± .71% and 15.08 ± .77% is 1.05%. The actual difference (2.56%) is 2.44 times the standard error of the difference. Such a difference in one direction could occur 7 times in 1000 as a matter of chance and, therefore, the difference is statistically significant.

The standard error of the difference between 3.01 ± .36% and 3.75 ± .40% is .54%. The actual difference (.74%) is 1.37 times the standard error of the difference. Such a difference in one direction could occur 85 times in 1000 as a matter of chance and, therefore, the difference is not statistically significant.

To make a stronger comparison, family histories of persons with low normal blood pressure were compared with those of persons

having high diastolic blood pressure. In the control group, there were 350 individuals past the age of 40, whose initial blood pressure was 120 mm., systolic, *and* 80 mm., diastolic, or less. There were 657 persons past the age of 40 in the hypertensive series whose initial diastolic blood pressure was 100 mm. (4th point), or more. As will be seen in Table 2, the incidence of familial hypertensive cardiovascular disease between the ages of 40 and 65 was 12.9% in persons with low normal blood pressure, as compared with 16.9% among those with high diastolic blood pressure. Even when persons with these extremes of blood pressure were studied, the difference in the incidence of familial hypertensive cardiovascular disease was not great.

TABLE 2.—COMPARISON OF FAMILY HISTORY IN APPLICANTS WITH LOW NORMAL BLOOD PRESSURE AND THOSE WITH HIGH DIASTOLIC PRESSURE

	No. of subjects Ages 40 to 65	One or more cases of hypertensive cardiovascular disease among parents and siblings	
		No.	%
Initial blood pressure 120 *and* 80 or less	350	45	12.86 ± 1.79
Initial diastolic blood pressure 100 or more	657	111	16.89 ± 1.45

The standard error of the difference between 12.86 ± 1.79% and 16.89 ± 1.45% is 2.30%. The actual difference (4.03%) is 1.75 times the standard error of the difference. Such a difference in one direction could occur 40 times in 1000 as a matter of chance, and, therefore, the difference may be statistically significant.

Family History of Diabetes. Some investigators have included familial diabetes with the cardiovascular diseases, but in this study diabetes was counted separately. Table 1 shows that 3% of the control subjects and 3.7% of the hypertensive applicants had a family history of diabetes. Since the difference is not statistically significant, it appears likely that a family tendency toward diabetes is not related to the subsequent development of hypertension.

Comment. By clinical concepts, the subjects were inadequately studied. It is impossible to classify the hypertension observed, but it is widely held that 80 to 90% of arterial hypertension is due to so-called essential hypertension. The determination of blood pressure is a simple procedure which can be accurately performed by most insurance examiners. Any inaccuracies would be offset by the large number of subjects involved. The well-known fact that persistent elevation of the blood pressure, as found on insurance examinations, has been associated with high death rates, and that normal blood pressure leads to normal death rates, validates blood pressure readings obtained on insurance examinations. More extensive clinical study would be desirable, but it is not necessary for comparative purposes.

It is important to know that the family history was not elicited more searchingly in the hypertensive group than it was in the control subjects. In the present series, it is reasonable to assume that the family history was recorded with about the same degree of care in each group. It is illogical to make a statistical comparison

without taking into account the obvious fact that the incidence of positive family histories is higher among the old than among the young. This is clearly shown by examining the records of the 2188 persons with normal blood pressure, as shown in Table 3. In this *control* group, the incidence of a positive family history of cardiovascular-renal disease was 10.8% in the 2d and 3d decades of life, 28.7% in the 4th and 5th decades, and 42.6% in the 6th and 7th decades. In the hypertensive subjects, similar age variations were observed.

TABLE 3.—INFLUENCE OF AGE ON FAMILY HISTORY IN 2188 APPLICANTS WITH NORMAL BLOOD PRESSURE

Ages	Subjects	One or more cases of cardiovascular-renal disease among parents and siblings	
		No.	%
10–29	397	43	10.83 ± 1.56
30–49	1119	321	28.69 ± 1.35
50–65	672	286	42.56 ± 1.91

A critical examination of the published material raises doubts as to the significance of heredity in the development of hypertension. Certainly, the figures reported here do not support the contention that it is of major importance. In this paper, the strongset possible comparison was made, *i. e.*, between the family histories of persons with low normal blood pressure and of subjects with high diastolic blood pressure. Surely, if hypertension is primarily a familial disease, a major variation in the incidence of hypertensive family histories should be observed, and yet only a slight difference was noted. Perhaps factors other than inheritance will be proved to be the cause of most cases of essential hypertension.

Summary. A brief review of the literature and analysis of family histories taken from life insurance examinations are reported. In this series of 4376 applicants, the incidence of familial cardiovascular disease was only slightly greater among hypertensive persons than it was among persons with normal blood pressure. There was no significant difference in the familial incidence of diabetes. It appears unlikely that heredity is of primary importance in the etiology of hypertension.

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THE EFFECT OF ANTIPRESSOR KIDNEY EXTRACT, ANGIOTONIN, METHYL GUANIDINE AND TYRAMINE ON CARDIAC OUTPUT AS MEASURED BY THE BALLISTOCARDIOGRAPH IN HYPERTENSIVE AND NORMAL PERSONS

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The action of angiotonin on both isolated and intact hearts reproduces some of the physiologic phenomena which have come to be associated with the cardiodynamics of arterial hypertension in man. Methyl guanidine and tyramine also exhibited some properties not unlike those of angiotonin, while having other properties distinctly different. It seemed of interest to compare the effects of these three pressor agents both on cardiac output and the contour of the ballistocardiographic curve to ascertain which of the three more nearly fulfilled the requirements of the naturally occurring pressor agent in hypertensive patients.

The significance of these results would be strengthened if it could be shown that not only does angiotonin reproduce the ballistocardiographic curve common in hypertensives, but that lowering the hypertensive's blood pressure by means of angiotonin-destroying kidney extracts causes reversion to the curve characteristic of normotensives. It is, then, the province of this communication to explore further the possibility that angiotonin is the chemical mediator of experimental renal and human hypertension.

Methods. In addition to 15 hypertensions, to be considered later, 6 healthy young laboratory workers were given the pressor drugs angiotonin and methyl guanidine in intravenous infusions of normal saline to maintain a constant elevation of arterial blood pressure. Tyramine was given subcutaneously to the same persons. The antipressor renal extracts were prepared by Dr. O. M. Helmer and given as daily intramuscular injections to patients with malignant or essential hypertension. These patients had been studied for 6 months or more in the Lilly Clinic. Estimations of cardiac output were made with the ballistocardiograph using the area method of Starr, Rawson, Schroeder and Joseph.[1]* All tracings were taken after a 15-minute rest period and at least 2 hours after a meal. When absolute values are given, the correction of 18.5% is made as suggested by Cournand, Ranges and Riley[3] to make the ballistocardiograph values correspond with those obtained by the direct Fick method.

Results. 1. *Tyramine Injection.* Stroke volume increased from 49, 48 and 58 cc. to 63, 52 and 69 cc., in 3 normal persons when

* Recently Starr and Schroeder detected a mathematical error in their paper J. Clin. Invest., **19**, 438, 1940. This error was excluded in the calculation of these data.

hypertension was induced by injection of tyramine. Calculated on the basis of the reduced pulse rate (*i. e.*, 108, 68, 80 reduced to 68, 60 and 54 beats per minute), cardiac output was decreased in the 3 experiments.

TABLE 1.—EFFECT OF TYRAMINE, METHYL GUANIDINE SULFATE AND ANGIOTONIN ON ARTERIAL BLOOD PRESSURE, STROKE VOLUME, PULSE RATE AND CARDIAC OUTPUT* OF NORMAL YOUNG ADULTS

	Before				After			
Case	Blood pressure, mm. Hg	Stroke volume, cc.	Pulse rate	Cardiac output	Blood pressure, mm. Hg	Stroke volume, cc.	Pulse rate	Cardiac output
				1. *Tyramine*				
1	134/82	49	108	3.05	236/130	63	68	2.47
2	118/82	48	68	1.88	192/110	52	60	1.80
3	116/60	58	80	2.68	152/93	69	54	2.15
				2. *Methyl Guanidine Sulfate*				
1	100/60	64	72	2.66	132/94	57	58	1.91
2	124/72	53	76	2.33	158/94	46	56	1.48
3	96/70	40	82	1.90	160/110	34	54	1.06
				3. *Angiotonin*				
1	96/70	40	82	1.90	152/110	36	54	1.12
2	124/72	53	76	2.33	154/100	47	64	1.73
3	120/80	46	84	2.23	180/120	31	90	1.61
4	100/68	57	70	2.30	140/110	46	54	1.43
5	132/72	58	82	2.74	140/110	45	70	1.82
6	102/78	57	78	2.57	146/110	45	62	1.61

* In liters per minute per square meter of body surface.

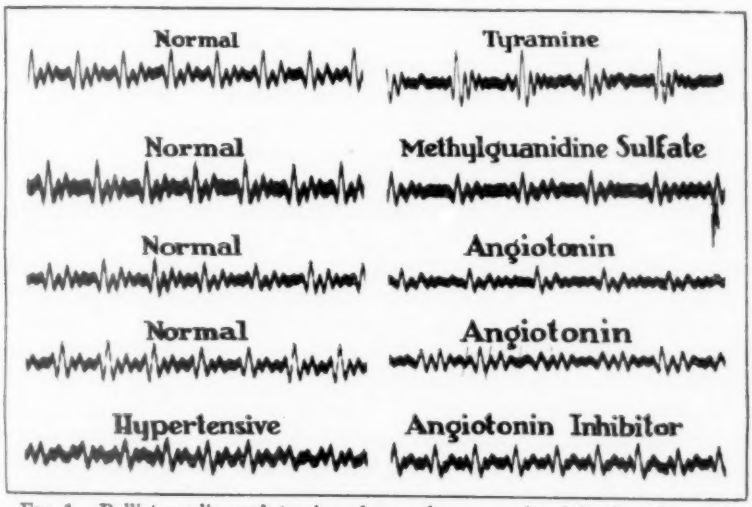

FIG. 1.—Ballistocardiograph tracing of normal persons after injection of tyramine (100 mg.), methyl guanidine sulfate (3 gm.) and angiotonin. The last pair of tracings are of a hypertensive patient before and after treatment with kidney extract.

The ballistocardiograph tracing of 1 of these subjects before and after injection of tyramine is illustrated in Figure 1. The blood

pressure before administration was 116/60 mm. Hg and after tyramine was 152/92 mm. Hg. The tracing clearly demonstrates the bradycardia as well as the increased stroke volume.

Of importance was the fact that highly unpleasant symptoms accompanied the hypertension. These began with consciousness of the slow, forceful beating of the heart, soon to be followed by almost unbearable headache and throbbing in the neck. The latter, along with nausea and vomiting, persisted though diminished in intensity, up to 6 hours.

2. *Methyl Guanidine Sulfate.* Methyl guanidine sulfate in amounts sufficient to produce similar elevation in arterial pressure decreased stroke volume instead of increasing it as did tyramine. But bradycardia also occurred, resulting in sharp fall in cardiac output (Table 1). These changes are seen in the second tracing in Figure 1. The arterial blood pressure rose in this subject after administration of methyl guanidine from 100/60 to 132/94 mm. Hg. The symptoms produced were not as severe as those with tyramine, but nevertheless very disagreeable. Tingling and numbness of the lips and mouth were followed by generalized numbness, precordial oppression, cold perspiration, faintness and nausea.

3. *Angiotonin.* Injection of angiotonin in 6 normal persons caused only slight bradycardia in 5 of the subjects. In the sixth the rate increased 6 beats per minute. But all of them exhibited decreased stroke volume (Table 1) and cardiac output. The third and fourth tracings in Figure 1 illustrate these changes in the ballistocardiographic record. It is of special interest that hypertension produced by angiotonin was not associated with marked symptoms. The bradycardia passed unnoticed.

4. *Contour of Tracings.* Comparison of the tracings in Figure 1 with Figure 3 show a difference in the form of the waves in some hypertensives as compared with normal subjects.

The waves following hypertension induced by tyramine differ strikingly from those observed in patients with essential hypertension. Those resulting from methyl guanidine differ less. Angiotonin, on the other hand, elicits ballistocardiographic waves closely resembling those seen in some hypertensive patients. As Starr has pointed out, however, the contour of the waves in hypertension is not characteristic of hypertension alone.

5. *Action of Kidney Extracts.* Twelve patients with malignant hypertension and 3 with essential hypertension were treated with antipressor angiotonin-destroying kidney extract in sufficient quantity to reduce arterial pressure (Table 2). The mean arterial pressure (diastolic + one-half the pulse pressure) of these patients before treatment was 174 mm. Hg with a maximum of 214 and minimum of 154 mm. Hg. The average cardiac output was 2.0 liters per minute per square meter of body surface. After treatment the average mean arterial pressure was 140 mm. Hg.

No increase in average pulse rate occurred. But the average cardiac output was increased from 2.0 to 2.5 liters per minute per square meter of body surface (Fig. 2).

TABLE 2.—EFFECTS ON ARTERIAL BLOOD PRESSURE, PULSE RATE, STROKE VOLUME AND CARDIAC OUTPUT OF ANTIPRESSOR RENAL EXTRACTS OF 15 HYPERTENSIVES

	Before				After				
Case	Blood pressure, mm. Hg	Pulse rate	Stroke volume	Cardiac output	Blood pressure, mm. Hg	Pulse rate	Stroke volume	Cardiac output	Diagnosis*
1	230/120	80	37	1.71	198/100	84	43	2.08	M
2	218/130	70	44	1.78	164/90	64	49	1.81	M
3	220/128	68	45	1.76	174/102	66	51	2.16	M
4	228/146	94	37	2.01	180/116	104	42	2.41	M
5	206/145	96	42	2.33	138/96	96	57	3.16	M
6	254/134	100	34	1.96	220/115	96	37	2.16	M
7	207/136	74	50	2.14	176/118	84	58	2.81	M
8	188/145	92	32	1.70	176/122	92	40	2.12	M
9	220/120	82	37	1.75	178/100	76	61	2.67	M
10	190/140	68	43	1.69	191/118	78	51	2.29	M
11	194/112	70	44	1.78	134/84	66	69	2.63	E
12	204/112	72	46	1.91	152/82	66	78	2.97	E
13	212/120	90	55	2.86	186/108	94	60	3.26	M
14	242/180	94	33	1.79	170/116	86	44	2.18	M
15	200/118	76	43	2.19	180/108	76	55	2.41	E

* E = Essential. M = Malignant.

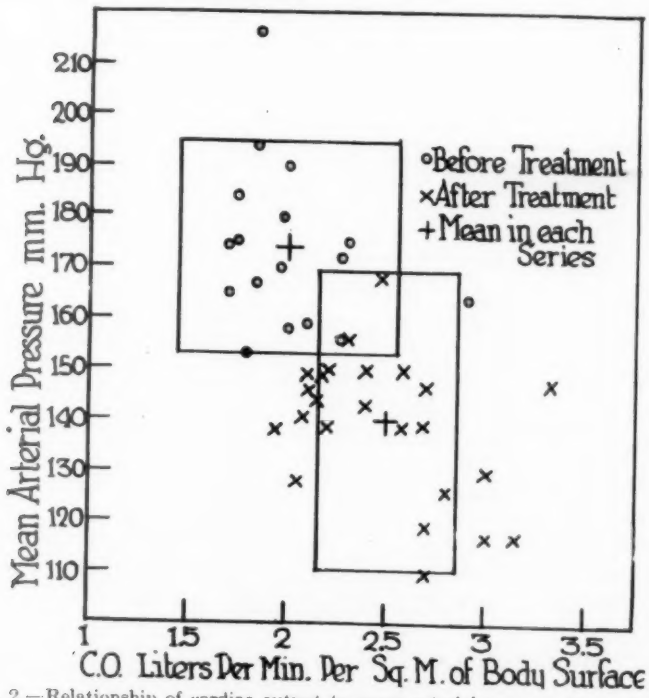

FIG. 2.—Relationship of cardiac output to mean arterial pressure (*i. e.*, diastolic pressure + one-half pulse pressure) before and after lowering the arterial pressure of hypertensive patients with kidney extract.

Inspection of the ballistocardiographic tracings before and after treatment clearly shows increase in stroke volume and absence of tachycardia (Fig. 4). When the "early M" complexes of Starr

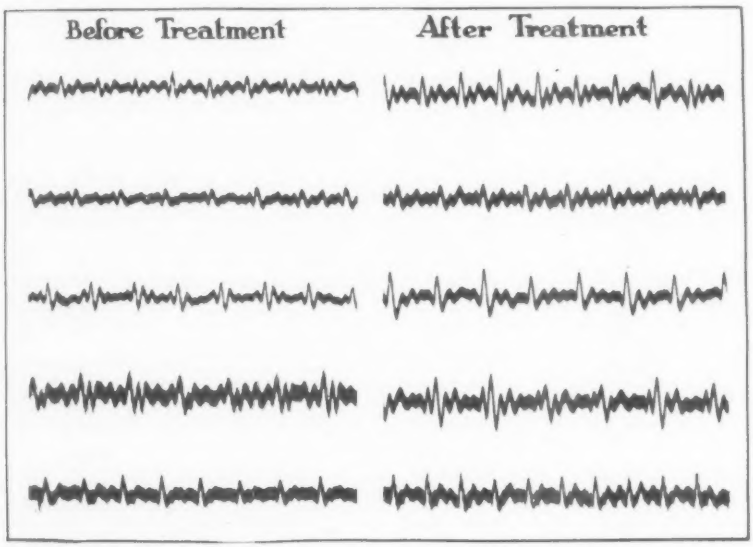

FIG. 3.—Ballistocardiographic tracing of 5 hypertensive patients before and after their arterial pressure was lowered by kidney extract.

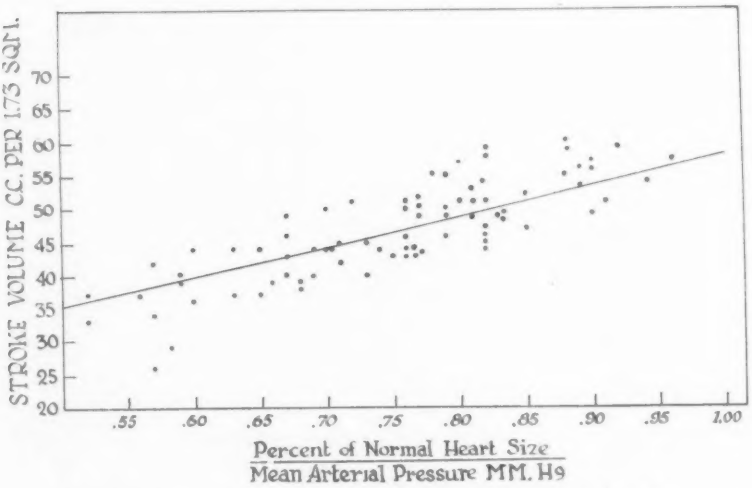

FIG. 4.—Relationship of stroke volume to $\frac{\text{cardiac enlargement}}{\text{mean arterial pressure}}$ $\left(\frac{\text{C.E.}}{\text{Pm}}\right)$ in 81 hypertensive patients.

were present before treatment they usually disappeared or were modified toward the form of the normotensive. This is especially clear in the first tracing in Figure 3. The average blood pressure of this patient before treatment was 206/145 mm. Hg, stroke volume 42 cc., and pulse rate 96 beats per minute. After treatment the blood pressure was 138/96 mm. Hg, stroke volume 57 and pulse rate 90. We believe the ballistocardiographic tracing taken after treatment to be normal in contour.

6. *Estimation of Stroke Volume.* The stroke volume as measured by the ballistocardiograph of a group of 25 healthy young adults is given in Table 3. These results are for comparison with those in Table 4 in which similar measurements on 81 hypertensive patients are recorded. In the latter table the results are arranged in relation to the mean arterial pressure. An attempt has been made, as will be discussed later in this communication, to estimate the stroke volume from a formula based on cardiac enlargement and mean pressure. It should be emphasized that these calculations are

TABLE 3.—STROKE VOLUME PER 1.73 SQ. M. OBSERVED IN 25 HEALTHY NORMOTENSIVE YOUNG ADULTS

Case	Mean arterial blood pressure, mm. Hg	Sex		Stroke volume per 1.73 sq. m. in cc.
1	80	F		55
2	80	F		55
3	80	M		57
4	84	F		53
5	84	M		57
6	88	M		59
7	89	F		53
8	90	M		57
9	93	M		62
10	94	F		58
11	95	F		52
12	95	F		55
13	95	M		65
14	98	F		55
15	99	F		53
16	100	F		52
17	100	F		51
18	100	M		66
19	104	F		52
20	104	M		60
21	108	M		56
22	109	F		49
23	109	M		58
24	109	M		57
25	112	M		63
		12 M	13 F	
Average	96	59.8	53.3	56.4

recorded rather as a stimulus for further exploration of the problem rather than a solution. Application of the ballistocardiograph to clinical problems is admittedly in its infancy and interpretation of the curves may subsequently be greatly altered. Despite this, records of observation with this method seem of value at this time.

TABLE 4.—BALLISTOCARDIOGRAPHIC $\frac{\text{STROKE VOLUME}}{\text{1.73 SQ. M.}}$ COMPARED WITH ESTIMATED $\frac{\text{STROKE VOLUME}}{\text{1.73 SQ. M.}}$

$$\left[\text{S.V.} = \left(46.12 \times \frac{\text{C.E.}}{\text{Pm}}\right) + 12\right] \text{ and } \left[\text{S.V.} = \left(46.12 \times \frac{100}{\text{Pm}}\right) + 12\right].$$

Case	Type of hypertension*	Mean arterial pressure, mm. Hg	% of normal heart size	Heart size Mean pressure	Observed stroke vol. per 1.73 sq. m.	Estimated stroke vol. C.E. Pm.	Stroke vol. estimated from Pm only	Sex
1	E	110	125	1.14	69	65	54	M
2	M	116	105	.90	57	53	52	M
3	E	117	100	.85	47	51	51	F
4	M	119	115	.96	57	56	51	M
5	E	121	100	.82	47	50	50	M
6	E	123	85	.69	40	44	49	M
7	E	124	87	.70	44	44	49	F
8	M	126	100	.79	49	48	48	F
9	E	126	100	.79	46	48	48	M
10	E	127	115	.91	51	54	48	F
11	M	128	105	.82	45	50	48	M
12	E	128	105	.82	46	50	48	M
13	E	128	85	.66	39	42	48	F
14	M	128	115	.90	49	54	48	M
15	E	128	93	.72	51	45	48	F
16	M	130	110	.85	52	51	48	M
17	M	131	105	.81	49	49	47	M
18	E	132	123	.94	54	55	47	F
19	M	133	110	.83	49	50	47	M
20	M	133	110	.83	48	50	47	M
21	M	135	120	.89	56	53	46	M
22	E	137	120	.88	59	53	46	M
23	M	138	105	.76	51	47	45	M
24	E	139	125	.90	56	53	45	M
25	E	140	102	.73	45	46	45	F
26	E	141	130	.92	57	54	45	M
27	E	143	105	.73	40	46	44	M
28	M	143	110	.77	43	48	44	M
29	E	144	110	.76	43	47	44	M
30	E	144	128	.89	53	53	44	M
31	M	144	110	.76	44	47	44	M
32	E	145	128	.88	55	53	43	M
33	E	145	110	.76	43	47	43	F
34	M	146	120	.82	51	50	43	M
35	E	146	110	.75	43	47	43	F
36	M	146	120	.82	54	50	43	M
37	M	147	120	.82	58	50	43	M
38	M	147	130	.88	60	53	43	M
39	M	148	120	.81	53	49	43	F
40	M	148	105	.71	45	45	43	M
41	M	149	100	.67	40	43	42	F
42	M	149	110	.74	44	46	42	F
43	M	149	105	.71	42	45	42	F
44	M	150	125	.83	49	50	42	M
45	M	150	109	.67	49	42	42	F
46	M	152	120	.79	50	49	42	F
47	E	153	125	.82	44	50	42	M
48	M	154	105	.68	38	43	42	M
49	E	154	105	.68	39	43	42	F
50	E	155	120	.77	50	48	42	M
51	M	155	125	.81	51	49	42	M
52	E	156	120	.77	51	48	41	M
53	E	156	120	.77	49	48	41	M
54	E	157	105	.67	43	43	41	M
55	M	157	125	.80	51	49	41	F
56	M	158	110	.70	44	44	41	M
57	E	158	120	.76	46	47	41	M
58	M	159	110	.69	44	44	41	M
59	E	159	100	.63	44	41	41	F
60	E	159	128	.80	57	49	41	M
61	M	165	123	.78	55	48	40	M
62	M	165	130	.79	55	48	40	M
63	M	165	125	.77	43	48	40	M
64	E	165	135	.82	59	50	40	M
65	M	168	110	.65	37	42	39	F
66	M	168	100	.59	39	39	39	M
67	M	172	120	.70	50	44	39	M
68	E	174	105	.60	44	40	38	M
69	M	175	110	.63	37	41	38	F
70	E	176	135	.77	49	48	38	M
71	E	178	100	.57	42	38	38	F
72	E	178	105	.59	40	39	38	M
73	M	178	120	.67	46	43	38	M
74	E	180	100	.57	26	38	38	F
75	M	181	105	.58	28	39	37	F
76	M	184	110	.60	36	40	37	F
77	E	185	120	.65	44	42	37	M
78	M	187	105	.56	37	38	36	F
79	M	194	110	.57	34	38	36	F
80	M	201	105	.52	37	36	35	F
81	M	211	110	.52	33	36	34	M

* E = Essential. M = Malignant.

Discussion. The broad problems in which the data in this communication are a small part consist in the search for a substance with physiologic properties consonant with those of a substance which might cause renal hypertension in animals and essential hypertension in man. Our studies were directed chiefly to the effects of angiotonin on the cardiac output and the contour of the ballistocardiographic tracing in normal man and a comparison of these with the pressor substances tyramine and methyl guanidine sulfate. These two drugs were selected among the many others because study of their effects on the arterioles of rabbit's ears demonstrates that they, in common with angiotonin—though to a much less degree—cause arteriolar constriction of a sort in which arterial pressure rises, but without appreciable reduction in blood flow to the tissues (Abell and Page[1]). Since we observed similarity in the cardiodynamics as recorded by the ballistocardiograph of hypertensive patients and in normal subjects with hypertension elicited by injection of angiotonin, it seemed desirable to ascertain whether reduction in blood pressure by means of antipressor and, perhaps significantly, angiotonin neutralizing kidney extracts, caused reversal to a more normal status.

Tyramine increased stroke volume somewhat but greatly reduced the heart rate, resulting in slight reduction in cardiac output. Methyl guanidine decreased stroke volume as well as reducing the heart rate, resulting in sharp reduction of cardiac output. Both substances produced most disagreeable symptoms even when the blood pressure was only moderately elevated. Contrasting with this is the fact that angiotonin decreased stroke volume but with only very moderate decrease in heart rate and marked reduction of cardiac output. Despite sharp elevation in blood pressure symptoms ordinarily do not appear.

The effects of angiotonin on the cardiovascular system in human beings have been made the subject of careful inquiries by Wilkins and Duncan,[9] and Bradley and Parker.[2] Both groups demonstrated reduction in cardiac output and increase in venous pressure. Bradley and Parker conclude that, since Roentgen ray studies failed to show cardiac dilatation, the failure of the heart to increase its size in the face of increased venous pressure is attributable to increased "cardiac tone." This conclusion was further supported by the observation of Lorber,[5] and Hill and Andrus,[4] that in isolated perfused hearts there is decrease in the diastolic volume when angiotonin is injected. On the other hand, Wilkins and Duncan found an increase in cardiac size and other evidences of "myocardial failure" in otherwise normal persons.

It cannot be decided with certainty from the data available whether the injection of angiotonin reproduces the cardiac changes observed in either experimental or spontaneous hypertension. The latter differs certainly in that venous pressure is not increased. It

may well be, however, that during the brief periods of angiotonin injection, time is not allowed for adaptation to occur.

As regards the decreased cardiac output, Starr has observed this, as measured by the ballistocardiograph, in a considerable number of patients with essential hypertension. Our own results in 81 hypertensive patients also show reduction in stroke volume, the average being 46.8 cc., with an average cardiac output of 2.14 liters per minute per square meter of body surface, as compared with 56.4 cc. and 2.28 liters per minute per square meter for 25 healthy, normotensive adults (Table 4). Cardiac output may be normal simply because the rate of the heart beat has increased.

Wilkins and Duncan[9] point out that the hypertension associated with acute nephritis has great similarity to that elicited by angiotonin. Both are characterized by elevation of venous pressure. The similarities may be brought to the fore by the fact that both occur within a brief space of time.

Bradley and Parker[2] found the cardiac output reduced chiefly as the result of bradycardia with little change in stroke volume when single injections of angiotonin were given. Our results, on the other hand, suggest the importance of reduction in stroke volume and less so the bradycardia.

Evidence gained from study of the isolated perfused heart, while not directly transferable to intact animals, nevertheless, is of importance. Hill and Andrus[4] found that angiotonin decreased coronary blood flow and increased the amplitude of the beat without any significant effect on the rate of cats' hearts. It augmented the output and the "arterial" pressure within the perfusion system; here, too, without influencing rate. They conclude that angiotonin causes direct stimulation of the myocardium and augmentation of the ventricular beat.

Lorber[5] observed constriction of the coronary arteries, decrease in the diastolic volume and increase in oxygen consumption, external work and efficiency of the heart in the isolated cat's heart. The fact that the vasoconstrictor and efficiency-increasing properties of angiotonin disappear with about the same dose, suggests that if the substance is liberated *in vitro* in sufficient quantity to exert one effect, it will probably exert the other as well.

When arterial pressure is lowered as the result of administration of kidney extract definite increase in cardiac output occurs. It seems reasonable to suppose that this is in part due to the decreased head of pressure against which the heart must work to eject its blood, resulting in more complete emptying of the ventricles. Since venous pressure does not rise when the arterial pressure falls, it is doubtful that increased filling of the heart plays any important part.

It may be of interest to speculate on the factors which influence cardiac output in hypertensives. One of these is the size of the heart, a second, the efficiency of ejection and the economy of effort with

which this is performed, and a third, the resistance against which the heart must work to expel blood. In most hypertensives the size of the heart is increased, but how much of this increase is due to increased diastolic volume, to hypertrophy, or to both, is not known. It is probable that this increased size helps in maintaining the cardiac output against an increased head of pressure. The hypertensive heart utilizes its ejection energy just as economically, and oftentimes more economically, than does the normal heart according to results of Wright, Hallaran and Wiggers[10] based on reconstruction of the ejection phase of intraventricular pressure from the subclavian pulse curve for contour and brachial arterial pressure. The surface area of the curve above the diastolic value divided by that beneath this area gives a quotient expressing the economy of ventricular effort during ejection. The resistance against which the heart works is obviously increased and is directly proportional to the mean arterial pressure.

We have attempted to correlate the stroke volume with the first and third of these factors, namely, cardiac enlargement and mean arterial pressure, in a group of hypertensive patients studied in the Lilly Clinic. We are only too well aware that even if a correlation could be arrived at, the result must be accepted with great reserve until the separate factors are proven to be measured with reasonable accuracy.

Cardiac enlargement (C.E.) is measured on the Roentgen ray film by the percentage deviation from the predicted normal established by Ungerleider and Clark.[8] Figure 4, drawn from the study of 81 hypertensive patients, suggests that a correlation exists (coefficient 0.718) when stroke volume corrected to 1.73 sq. m. of body surface is plotted against the $\frac{\text{per cent of cardiac enlargement}}{\text{mean arterial pressure}}$. It might thus be anticipated that the cardiac output in early hypertension with little cardiac enlargement would be comparatively low.

By means of regression equations it is possible to establish constants allowing formulation of the equation

$$\text{S.V.} = \left(46.12 \frac{\text{C.E.}}{\text{Pm}}\right) + 12$$

where S.V. = stroke volume corrected to 1.73 sq. m. of body surface, C.E. = percentage of normal cardiac size, and Pm = mean arterial pressure. Stroke volume as predicted from this formula corresponded fairly closely with that measured by the ballistocardiograph (Table 4). The mean deviation from the measured value was 12.5.

The most evident source of inaccuracy in the formula is the fact that the fraction $\frac{\text{C.E.}}{\text{Pm}}$ has only a small variation while the correction factor is large. Since the range of S.V. is also not great it can be questioned whether correlation between S.V. and $\frac{\text{C.E.}}{\text{Pm}}$ really exists.

If the observed Pm and S.V. values of Table 4 are arranged in descending order of Pm it is clearly seen that S.V. is inversely proportional to Pm. In short, as the pressure rises in hypertension, the stroke volume is decreased, which is what might be anticipated. If the factor of cardiac enlargement is added, the heart should perform its work against a higher resistance more capably and stroke volume fall off less than if cardiac enlargement were not included in the calculation. Of 81 determinations, the calculated value was closer to the observed when cardiac enlargement was included in the formula in 48 examples. In 10 examples, no difference would be anticipated as the heart size was normal, while in 23 the estimate was more accurate when it was omitted.

Starr, Donal, Margolies, Shaw, Collins and Gamble[7] pointed out that hypertensives with small hearts have stroke volumes smaller than normal. Since they have shown that the basal work per beat of the normal heart is a function of its size, *i. e.*, an extension of Starling's Law of the Heart to clinical conditions, it is not surprising that a relationship between stroke volume and $\frac{\text{C.E.}}{\text{Pm}}$ might be found.

Summary. 1. The effect of angiotonin, tyramine and methyl guanidine on cardiac output was studied in 6 normotensive young adults by means of the ballistocardiograph. Tyramine increased stroke volume and greatly reduced heart rate, resulting in slight reduction of cardiac output. Methyl guanidine decreased stroke volume and rate, resulting in sharp reduction of cardiac output. Angiotonin decreased stroke volume but reduced the rate only slightly, resulting in marked reduction of cardiac output. Tyramine produces severe symptoms, methyl guanidine less severe ones, and angiotonin almost none at all.

2. The cardiodynamics, as recorded by the ballistocardiograph when tyramine and methyl guanidine are injected, differ strikingly from those of patients with essential hypertension or after injection of angiotonin into normotensives.

3. Antipressor angiotonin-destroying kidney extract administered to hypertensive patients elevated cardiac output when the mean arterial pressure fell and the contour of the ballistocardiographic curves resumed a normal or near normal appearance.

4. Stroke volume and cardiac output as measured by the ballistocardiograph are definitely reduced in many hypertensive patients.

5. An attempt has been made to relate by means of a formula stroke volume with cardiac enlargement and mean arterial pressure.

Conclusions. The cardiac effects of tyramine, and less so of methyl guanidine, as measured by the ballistocardiograph are such as to make it unlikely that they participate in the genesis of renal hypertension. On the contrary, angiotonin exhibits properties which are consonant with those anticipated from knowledge of the cardiodynamics in hypertension. This view is strengthened by the

observation that antipressor, angiotonin-destroying extracts of kidneys administered to hypertensive patients abolish at least one characteristic action of angiotonin, *i. e.*, they increase the depressed cardiac output.

We wish to express our appreciation to Drs. Stanley Bradley, Homer Smith and Isaac Starr for their aid in this investigation.

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THE EFFECT OF A HIGH-FAT TEST MEAL ON BLOOD CHOLESTEROL IN NORMAL AND OBESE INDIVIDUALS

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Experimental evidence to the effect that the cholesterol content of the blood in human subjects may be altered by the ingestion of a meal high in cholesterol or fat (or both) remains conflicting. Widal, Weill and Laudat[24] noted a marked increase in blood cholesterol in healthy subjects fasting for 15 hours and then given a meal consisting of meat, potatoes, bread and 50 gm. of butter. In 10 of 11 healthy individuals fed a meal consisting of soup, bread, meat, green vegetables, 2 eggs and wine, Rouzaud *et al.*[19] found no increase in the blood cholesterol 4 to 5 hours after the meal. In one subject, an increase of 5% in the cholesterol content of the blood was observed. Luden[16] noted that whereas the ingestion of bread, butter and tea had no effect on blood cholesterol, a heavier meal consisting of bread, butter, tea, 1 egg and ½ cantaloupe produced an increase of 25 to 30%. Denis[10] reported no increase in blood cholesterol in 3 subjects after a meal high in fat.

Hiller, Linder, Lundsgaard and Van Slyke,[13] using a test meal consisting of butter (usually 1 gm. per kilogram) found no significant

increase in the whole blood or plasma cholesterol in 6 normal subjects and in 7 patients with nephritis. Bürger and Habs[7] observed large increases in serum cholesterol (up to 100%) after the ingestion of 100 gm. of olive oil and 5 gm. of cholesterol. Barreda[1] and Snapper and Parisel[22] utilizing the same diet were unable to confirm these results. Chaikoff, McGavack and Kaplan[8] found no increase in the free or combined cholesterol of the blood in 6 of 7 subjects following the ingestion of 100 ml. of olive oil; 1 subject showed an increase of 35% in the total cholesterol content of the blood 4 hours after the meal. Gardner and Gainsborough[12] reported no increase in blood cholesterol following a single meal high in cholesterol. Bruger and Somach[6] also observed that the ingestion of food had no appreciable effect either immediate or late on blood cholesterol.

Rony and Levy[18] found no increase in the cholesterol content of the plasma in 8 normal and 18 obese subjects after the ingestion of a test meal consisting of 500 ml. of 20% cream. Using the same test meal, Blotner[5] confirmed the lack of increase in blood cholesterol in normal persons but reported a marked rise in the blood cholesterol level in obese individuals. In subjects who were underweight, the blood cholesterol remained either unchanged or decreased. In patients with psoriasis and in non-dermatologic patients, LeWinn and Zugerman[15] reported marked increases in the total blood cholesterol following a test meal high in fat.

In view of these conflicting observations, this problem (alimentary hypercholesterolemia) was reinvestigated.

Material and Methods. Seven normal subjects (laboratory technicians) ranging in weight within 10% of the calculated normal weight were placed on a low fat and low cholesterol diet* for 2 days. On the morning of the 3d day, a fasting specimen of blood was taken and again at intervals of 1½ hours for 6 hours. During this time, the subjects followed the prescribed diet and continued their usual activities. After this initial study, they remained on the low fat and low cholesterol diet for 2 more days. On the 6th day, a fasting specimen of blood was again taken and a test meal consisting of 500 ml. of cream (20% fat) was given. Blood specimens were taken again at intervals of 1½ hours for 6 hours. No food other than the test meal was permitted during this second phase of the experiment.

Thirteen subjects who were from 23% to 92% overweight were placed on the low fat and low cholesterol diet for 2 days. On the morning of the 3d day, a fasting specimen of blood was taken and the test meal given. Blood specimens were obtained at intervals of 1½ hours for a period of 6 hours.

The total and free cholesterol content of the serum was determined by the Schoenheimer and Sperry method[21] as modified by Fitz[11] and adapted for the photoelectric colorimeter. In addition, the total cholesterol content of the whole blood, plasma and saline-washed red blood cells was determined by a modified Bloor procedure.[17,20] The serum of 3 obese subjects was also analyzed for total lipids and fatty acids by the method of Bloor.[4]

* Milk, cottage cheese, lean beef, lamb, chicken or fish, clear broth, cooked cereals, white bread, potatoes, macaroni, noodles, rice, spaghetti, vegetables, fruits, gelatin, junket, coffee or tea.

TABLE 1.—VARIATIONS IN THE TOTAL AND FREE CHOLESTEROL CONTENT OF THE SERUM IN 7 NORMAL SUBJECTS ON A DIET LOW IN FAT AND CHOLESTEROL AND AFTER A TEST MEAL HIGH IN FAT

Subject	Age and sex	% over or under weight	Low fat and low cholesterol diet: Total cholesterol* mg./100 cc.							Low fat and low cholesterol diet: Free cholesterol* % of total					High fat test meal: Total cholesterol* mg./100 cc.							High fat test meal: Free cholesterol* % of total				
			Fasting	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	+†	−†	Fasting	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	Fasting	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	+	−	Fasting	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.
E. R.	20 F	0	200	200	184	188	190	0	8.0	26	25	25	25	25	194	194	192	199	207	8.2	1.0	31	28	28	28	27
E. F.	25 F	− 6	254	256	250	240	238	0.8	6.0	27	27	26	27	25	240	238	227	234	225	0	6.3	27	29	29	31	29
S. E.	24 F	+ 3	208	205	231	201	203	10.5	3.3	24	24	27	26	26	183	188	186	184	200	8.5	0	29	27	28	29	27
M. D.	27 M	+ 9	270	270	263	260	265	0	3.7	26	26	27	25	26	278	280	268	265	265	0.7	4.6	27	26	28	28	27
A. A.	24 F	−10	180	186	178	194	176	7.8	2.3	27	25	25	24	25	175	195	188	170	182	10.8	2.8	28	28	29	30	29
A. H.	22 F	− 6	168	168	162	175	159	4.0	5.9	26	25	27	26	27	176	182	181	175	164	2.8	6.8	26	24	26	26	28
M. Mc.	22 F	− 4	157	160	145	160	161	2.5	7.6	24	24	25	24	25	159	158	158	151	151	0	5.0	23	24	24	27	27
Mean	..	..	205	206	202	203	199	3.8	5.3	26	25	26	25	26	201	205	200	197	199	4.4	3.8	27	27	27	28	28

* Method of Schoenheimer-Sperry.[11,21]

† Per cent deviation from fasting level.

Results and Comments. In 7 subjects with normal body weight, the ingestion of a diet low in fat and cholesterol or a test meal high in fat failed to influence the total cholesterol content of the serum over a period of 6 hours (Table 1). On the low fat and low cholesterol diet, the maximal deviations from the fasting level of the total serum cholesterol ranged from +10.5% to −8% with a mean of +3.8% to −5.3%. On the high fat test meal, the maximal deviations ranged from +10.8% to −6.8% with a mean of +4.4% to −3.8%. The findings confirm the early observations of Bloor[3] and Knudson[14] in dogs but are at variance with some observations in humans.[7,15,16,24] In two instances, the test meal high in fat resulted in a decrease rather than an increase in the total serum cholesterol; this phenomenon was previously described by Barreda[1] and Gardner and Gainsborough.[12] Table 1 also shows the remarkable constancy of the free cholesterol expressed as per cent of the total cholesterol on both dietary régimes, an observation previously recorded by Sperry.[23]

TABLE 2.—VARIATIONS IN THE TOTAL AND FREE CHOLESTEROL CONTENT OF THE SERUM IN 13 FEMALE OBESE INDIVIDUALS AFTER A TEST MEAL HIGH IN FAT

Subject	Age	% Overweight	Associated clinical conditions	Total cholesterol* mg./100 cc. Fasting	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	+†	−†	Free cholesterol* % of total Fasting	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.
J. M.	46	59	Synovitis left knee	207	200	219	194	200	5.8	6.3	26	26	25	28	27
M. G.	44	47	None	236	238	242	240	240	4.2	0	27	26	25	27	28
Y. P.	49	65	None	236	214	227	230	242	2.5	9.7	28	27	26	27	26
R. C.	49	92	None	268	258	248	252	250	0	7.1	26	28	29	28	28
S. P.	37	36	Hypertension	337	326	322	319	330	0	5.3	25	27	27	28	29
N. W.	55	46	Hypertension	256	254	258	273	258	6.6	0.8	29	31	29	29	31
M. S.	18	55	None	200	201	197	196	197	3.5	2.0	25	26	26	29	28
R. L.	23	23	None	225	219	205	208	214	0	8.9	25	25	26	26	25
M. F.	42	23	Varicose veins	320	312	304	320	329	2.8	5.0	27	26	27	26	25
E. G.	47	41	Phlebitis	254	263	268	261	263	5.5	0	27	27	27	27	28
C. R.	33	26	None	273	270	273	263	286	4.8	3.7	28	28	28	28	27
C. S.	49	39	None	273	270	258	265	283	3.7	5.5	25	26	27	27	27
E. H.	40	50	Varicose veins	205	205	205	210	217	5.9	0	26	25	27	25	27
Mean	..	..	...	253	248	248	248	254	3.5	4.2	26	27	27	27	27

* Method of Schoenheimer and Sperry.[11,21]
† Per cent deviation from fasting level.

In 13 obese women, the ingestion of a meal high in fat likewise was without effect on the total cholesterol content of the serum over a period of 6 hours (Table 2). The maximal deviations from the fasting level of the total serum cholesterol ranged from +6.6% to −9.7% with a mean of +3.5% to −4.2%. These findings failed to confirm those of Blotner[5]; he noted a marked increase in blood cholesterol in obese individuals following the ingestion of 500 ml. of 20% cream (the test meal used in this study). Of interest is the finding in this series that not only did the serum cholesterol fail to rise significantly after the high fat test meal but in 3 of the 13 observations, a decrease in serum cholesterol was demonstrated.

The constancy of the free cholesterol noted above was again observed.

In this study, 2 methods for the determination of blood cholesterol were used. Emphasis is placed on the Schoenheimer and Sperry method[21] (Tables 1 and 2) since this procedure is conceded to be the most accurate colorimetric method available today for determining this constituent of the blood. However, since many of the published reports on this subject utilized the original[2] or a modified Bloor procedure,[20] this method was also employed in this investigation (Table 3). In general, the results obtained with both methods were similar, though greater individual variations in the total cholesterol were observed with the latter procedure. Table 3 shows that in subjects with normal or increased body weight, no significant alteration in the total cholesterol content of the whole blood, plasma and saline-washed red blood cells was observed after a test meal high in fat.

TABLE 3.—VARIATIONS IN THE CHOLESTEROL CONTENT OF WHOLE BLOOD, PLASMA AND SALINE-WASHED RED BLOOD CELLS IN 7 NORMAL SUBJECTS AND IN 13 OBESE INDIVIDUALS ON A DIET LOW IN FAT AND CHOLESTEROL AND AFTER A TEST MEAL HIGH IN FAT

(SUMMARY TABLE OF AVERAGE VALUES)

Experiment	Total cholesterol* mg./100 cc.					% deviation from fasting level	
	Fasting	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	+	−
Normal subjects							
Low fat and low cholesterol diet							
Whole blood	164	170	171	166	169	4.3	0
Plasma	166	165	162	163	166	0	2.4
Red blood cells	120	125	119	133	113	10.9	5.9
High fat test meal							
Whole blood	164	167	167	161	170	3.6	1.8
Plasma	166	165	164	167	165	0.6	1.2
Red blood cells	109	108	115	113	114	5.5	1.0
Obese subjects							
High fat test meal							
Whole blood	193	190	196	194	193	1.5	1.5
Plasma	196	193	190	192	197	0.5	3.1
Red blood cells	124	128	125	124	121	3.2	2.4

* Modified Bloor method.[17,20]

In 3 obese individuals, it was further demonstrated (results not tabulated) that the ingestion of a test meal high in fat increased appreciably the total lipids and fatty acids in the serum as previously noted by Cowie and Hoag[9] and Rony and Levy.[18]

Conclusions. 1. In subjects with normal body weight, the ingestion of a diet low in fat and cholesterol or a test meal high in fat (500 ml. of 20% cream) failed to alter the cholesterol content of the serum, whole blood, plasma and saline-washed red blood cells over a period of 6 hours.

2. In obese women, a test meal high in fat was followed by significant increases in the concentration of total lipids and fatty

acids in the serum but failed to influence the total cholesterol content of the serum, whole blood, plasma and saline-washed red blood cells.

3. The free cholesterol content of the serum expressed as per cent of the total cholesterol remained remarkably constant in normal and obese individuals on both dietary régimes.

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LEUKOCYTOSIS INDUCED BY METHYL–ACETAMIDE WITH P–CHLORO–XYLENOL

Chemotactic Effect on Bone Marrow

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It is well known that bone marrow reacts to various chemical and biologic substances with the formation and liberation of leukocytes. This exaggerated activity is expressed by an increase in the number of leukocytes in the peripheral blood. Among the chemical substances possessing this property, nucleinic acid and its derivatives (adenin and guanin) are the best known. Their employment in various leukopenic conditions, however, has given only transitory results, their effect being limited to the liberation of mature leukocytes but with no stimulus to their new formation. Furthermore,

leukocytosis resulting from the injections of nucleinic acid is preceded by a brief leukopenia, thus limiting its use in severe agranulocytosis. This undesirable effect is avoided by the use of pentose nucleotide.

Powers, Murphy and Humphreys[2] (1933) have described a leukocytosis provoked by injections of hepatic extract. This leukocytosis is of short duration and has given no results in the treatment of granulocytopenic conditions[1] (typhoid, agranulocytosis, and so forth).

Exogenic chemical substances, like collargol and pyrogallol, are also able to provoke leukocytosis in a normal individual, but have little effect in leukopenic conditions. These substances have not been introduced in therapeutics because their leukocytosis effect is often followed by periods of granulopenia due to inhibition of the leukopoietic function.

During investigations on the chemotherapeutic use of halogenized phenols (Zondek[3]), the solubility of p-chloro-xylenol in various substances was studied. Among these was methyl-acetamide,* which in contradistinction to other solvents, induced a distinct leukocytosis in the blood stream when injected intramuscularly.

Methyl-acetamide produced a leukocytosis of short duration, but the combination of methyl-acetamide with p-chloro-xylenol was found to prolong and strengthen considerably the leukopoietic effect. It should be mentioned that p-chloro-xylenol alone has no influence on the leukocytic function of bone marrow (Zondek[3]).

Methods. It is well known that the number of leukocytes in a normal individual undergoes important fluctuations during the day, being lowest about 11 A.M. and 11 P.M. and highest at about 5 A.M. and 5 P.M. In the normal individual more than 10,000 leukocytes were never found at any time.

The leukocytic counts were performed at fixed hours—11 A.M. and 6 P.M. The results are the average of at least two separate counts. The drug was regarded as producing a positive effect when the count rose to over 10,000. All physiologic factors influencing the number of circulating leukocytes were eliminated as far as possible. All persons examined were admitted to hospital, lay in bed and received a constant diet. Muscular effort was strictly forbidden. In each case the normal number of leukocytes was determined for several days, before beginning the treatment. The substances studied were administered at the same time of the day, to all subjects.

The following products were examined for their chemotactic effect:

1. A 70% solution of methyl-acetamide (referred to as "M").
2. A 70% solution of methyl-acetamide with 15% p-chloro-xylenol (referred to below as "15% CXM").
3. A 70% solution of methyl-acetamide with 25% p-chloro-xylenol (referred to below as "25% CXM").
4. A 10% solution of p-chloro-xylenol in oil.

The studies were performed on 25 persons, of whom 17 were normal, 4 suffered from typhoid fever with leukopenia, and 4 had local infections with leukocytosis.

* We are indebted to the Teva, Middle East Pharm. & Chem. Works, Ltd., Jerusalem, for their kind supply of methyl-acetamide and p-chloro-xylenol.

Studies in Normal Subjects. A. *Leukopoietic Effect of Methyl-acetamide.* Deep intramuscular injections of 10 cc. of methyl-acetamide, in the normal individual, produce after 24 hours a leukocytosis which is about 60% higher than the highest preceding

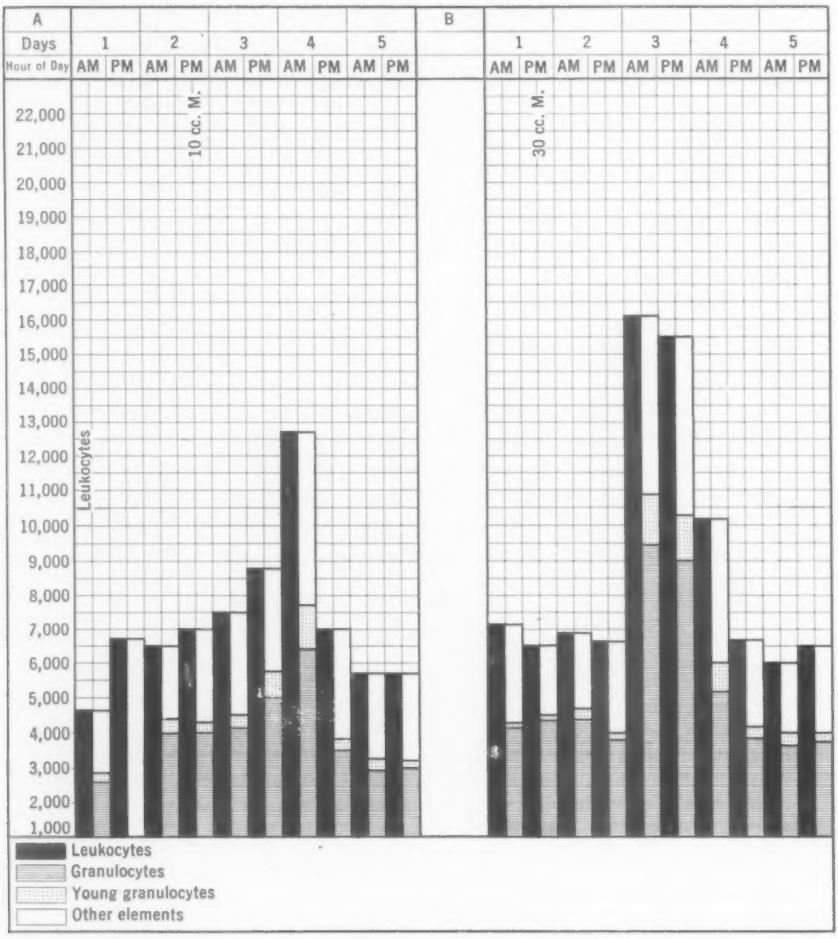

CHART 1.—Number and distribution of leukocytes after 10 cc. and 30 cc. of methyl-acetamide.

leukocyte count (Chart 1, *A*). This leukocytic reaction is in direct proportion to the dose of methyl-acetamide given: thus, 30 cc. of this substance have induced a leukocytosis of double the original number of leukocytes and of somewhat longer duration than do 10 cc. (Chart 1, *B*). This leukocytosis is due especially to an increase

in the number of younger forms of granulocytes. Methyl-acetamide alone, as a leukocytosis producing factor, is not suitable for practical purposes, because large doses are required to induce a prolonged leukocytosis.

B. *Leukopoietic Effect of Methyl-acetamide Combined with p-chloro-xylenol.* Injections of 10 cc. methyl-acetamide with 15% p-chloro-xylenol induce an increase in the number of leukocytes, 80% higher than the initial counts. This leukocytosis is due especially to the granulated elements, and reaches its maximum 48 hours after injection. Leukocytosis of similar character but still higher and more prolonged is obtained by injections of methyl-acetamide solutions with 25% p-chloro-xylenol. Ten cubic centimeters of this product provoke a rise in the leukocytic count beginning 24 hours after injection, reaching the maximum (double the original number) after 48 hours and lasting for a further 48 hours.

The injection of 10% p-chloro-xylenol in oil did not induce leukocytosis in normal individuals. On the other hand, it has been shown that the addition of p-chloro-xylenol to methyl-acetamide (CXM) increases the latter's chemotactic effect on leukocytosis, which is stronger in proportion with the concentration of p-chloro-xylenol.

It should be emphasized that the leukocytosis induced by these substances is not preceded by nor followed by leukopenia.

We attempted to produce a prolonged leukocytosis with methyl-acetamide in 25% p-chloro-xylenol (25% CXM). Fifty cubic centimeters of this solution, given over 3 days, induced leukocytosis (over 10,000) of 10 days duration and with maximal counts of 20,200. This leukocytosis was due especially to the neutrophils which increased more than fourfold in absolute numbers, their proportion to the other white blood corpuscles increasing from 72 to 80%. In another case (Chart 2) 70 cc. of the same product (25% CXM), given over 3 days, caused a leukocytosis of 10 days duration, with an enormous rise in leukocytes reaching its maximum (30,200) on the 4th day after the beginning of injections.

Studies in Patients with Leukopenia. The effect of 25% CXM in leukopenic conditions was investigated in 4 typhoid cases (the only leukopenic conditions at our disposal).* The leukopenia in typhoid, which is due to the inhibition of the granulopoietic function of the bone marrow, is particularly resistant to chemotactic substances. In these cases also it was possible to induce leukocytosis with 25% CXM. Here, however, the antagonistic action of the bone marrow is indicated by the need for higher doses and the short duration of leukocytosis. A 7-year-old boy received 56 cc. of 25% CXM during 5 days, which increased the leukocyte count from 5000 to 12,000, the increase of neutrophils paralleling that of the leukocytes.

* We are indebted to Dr. Gruenfelder, Head of the Pediatric Department, for putting these cases at our disposal.

In another case, a 10-year-old boy, the rather high dose of 72 cc. of 25% CXM given over 5 days, induced a neutrophilic leukocytosis, reaching a maximum of 32,400 on the 5th and 6th day after beginning of treatment (Chart 3). The leukocytic count, however, had dropped to the initial level 36 hours after stopping treatment.

In normal patients whose bone marrow is not depressed as it is in typhoid fever, the increased leukocyte count persists for about 10 days.

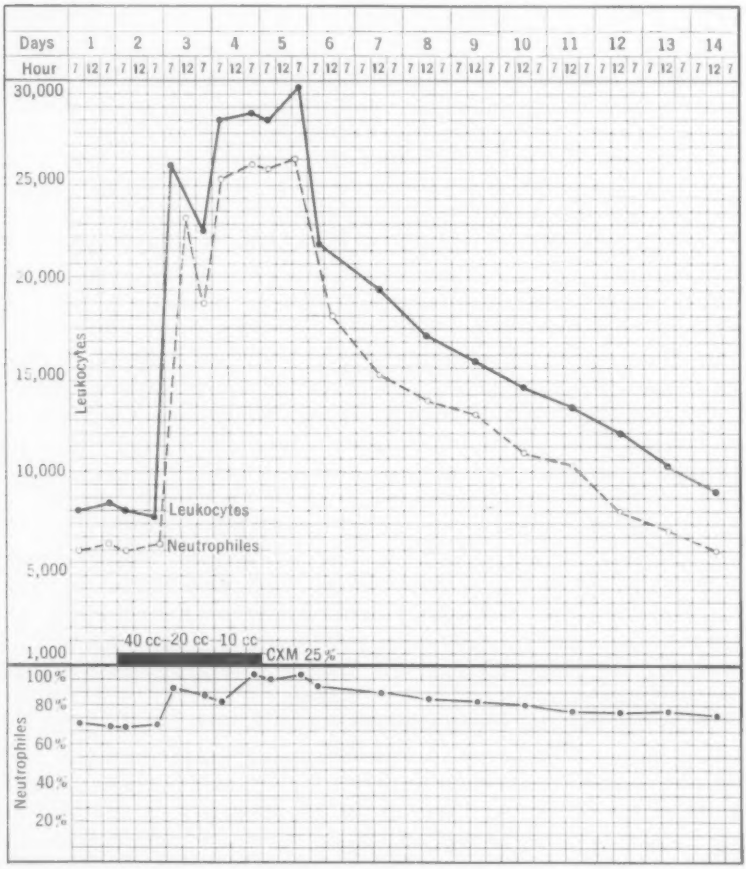

CHART 2.—Leukocyte changes after 70 cc. of 25% CXM.

Studies in Patients with Leukocytosis. In cases of inflammatory conditions with leukocytosis the response to methyl-acetamide seems to be more prompt than in normal conditions. For instance, a case of pyelitis with a count of 9200 reacted to injection of 25% CXM with a leukocytosis of 38,000.

Qualitative Changes in the Leukocytic Picture Induced by CXM Treatment. It is well known that an increase in neutrophils in the peripheral circulation is due to their increased production in the bone marrow. Nevertheless, this rule is subject to certain exceptions. Thus, the spleen is thought to be able, in certain conditions, to accumulate or liberate leukocytes with resulting phases of leuko-

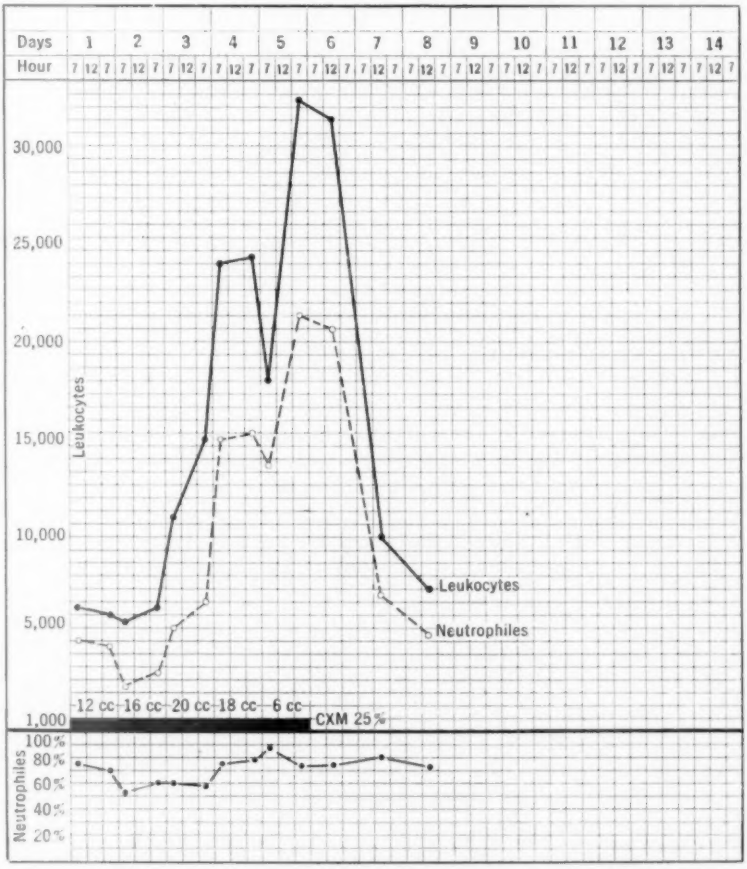

CHART 3.—Leukocytosis produced by CXM in typhoid leukopenia.

penia and leukocytosis (leukocytosis due to redistribution). In order to determine whether the leukocytosis obtained after the injection of CXM was due to redistribution or to direct stimulation of the bone marrow, the qualitative study of the neutrophils was necessary. In the former case the white differential count is that of normal blood, while in the latter the young cells driven from the center to the peripheral blood shift the differential count to the left.

CXM, when given in sufficient quantities, induces leukocytosis with a clear shift to the left. This occurred in all 25 cases. As an example, the Schilling's hemogram of 1 case is reported below (Table 1). The leukocytosis rises from 9200 up to 38,000. The qualitative blood study reveals a distinct shift to the left. The number of young and band forms increased, while the myelocytes were not found in the peripheric blood.

TABLE 1.—LEUKOCYTOSIS WITH SHIFT TO THE LEFT INDUCED BY CXM

	Before treatment	After treatment with 70 cc. of 25% CXM
Leukocytes	9,200	38,000
Basophils		
Eosinophils	1	
Neutrophils:		
Myelocytes		
Young forms	..	3
Band forms	1	13
Segment	79	62
Lymphocytes	17	14
Monocytes	1	1

The number of young forms of neutrophils in circulation permits the evaluation of the effect of CXM on bone marrow. The age of neutrophils was determined according to Arneth's method, where the ratio between the monolobar and segmented neutrophils (nuclear shift index) is proportional to the extent of bone marrow stimulation by the substance used. Following treatment with large doses of CXM, the shift index, which is normally 6.2% (according to Schilling) was found to be about 25%.

In some cases, following excessively high doses of CXM, we found neutrophils with pyknotic nuclei or toxic granulated protoplasm—which might have suggested a degenerative process of the bone marrow. The sternal puncture performed during the peak of leukocytosis revealed a high percentage of band forms.

CXM was found to stimulate electively the granulopoietic function of the bone marrow, not affecting the other elements of the white series, erythropoiesis or thrombocytopoiesis. The strong and elective effect of CXM on the granulopoietic function of bone marrow allows one to expect favorable results in the treatment of neutropenic conditions. Moreover, CXM has the advantage of combining its chemotactic effect with the chemotherapeutic properties of p-chloro-xylenol (Zondek[3]). CXM may thus be indicated in cases of agranulocytosis secondary to general infection.

Studies in Animals. The chemotactic effect of CXM was studied in rats, hens and rabbits. The considerable fluctuations in the number of leukocytes in normal conditions in these animals make it difficult to reach any definite conclusion in these experiments. In hens, the leukocytes rose from 60,000 to 80,000 after 3 cc. of 25% CXM given during 6 days. In the rabbit the leukocytic count rose from 9000 to 13,000 following 10 cc. of 25% CXM given during

11 days. Nevertheless, the leukocytic level did not surpass that which is found in normal conditions.

Toxicity. The lethal dose of a 70% solution of methyl-acetamide (M) in mice weighing 16 gm. was found to be 0.2 cc., while the corresponding dose of 25% CXM was 0.1 cc. Rats weighing about 100 gm. show no disturbances after administration of 0.5 cc. of 25% CXM. Rabbits weighing 1100 to 1200 gm. can stand 1 cc. of 25% CXM daily, even when given for 10 days or more. In men, the highest dose which causes no complaints was 20 cc. 25% CXM daily (2 × 10 cc. daily). Higher doses cause local and general disturbances. Locally, we sometimes observed tissue necrosis and neuritis. Vomiting, probably of central origin, was also observed, following large doses. It should be emphasized that vomiting coincided with high leukocytic levels.

Dosage. The dose of 25% CXM necessary to induce a strong leukocytic reaction in men is: 2 injections of 10 cc. of 25% CXM during the first day and 1 injection of 10 cc. daily for the next 3 days. In order to avoid infiltrative reactions and discomfort, these injections should be given intragluteally in the deeper muscular layers and 2% anesthesin should be added.

Summary and Conclusions. 1. The chemotactic effect of methyl-acetamide alone and combined with p-chloro-xylenol was studied in 25 patients.

2. Methyl-acetamide injected intramuscularly induces leukocytosis, which reaches its maximum 24 hours after injection. This effect on leukopoiesis is proportional to the dose employed.

3. The injection of methyl-acetamide combined with p-chloro-xylenol (CXM) gives a much higher leukocytosis than that of methyl-acetamide alone. The leukocytic effect produced is proportional to the quantity of p-chloro-xylenol dissolved in methyl-acetamide.

4. In all the 4 cases of leukopenia in typhoid fever treated with injections of CXM, leukocytosis was induced.

5. The characteristic features of the leukocytosis produced by CXM are the shift to the left, with a significant increase in young and band forms. This supports the assumption that this leukocytosis is due to a stimulation of the granulopoietic function of bone marrow.

6. The results obtained in normal and in typhoid cases suggest the trial of these substances in neutropenic conditions.*

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* We have awaited a potent leukopoietic bone marrow stimulant ever since the leukopenic effect of mustard gas was demonstrated in World War I. We hope that the above study may start the solution of this problem.—Ed.

LIVER FUNCTION IN THERAPEUTIC MALARIA*

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Various effects of malarial infections upon the liver have been observed. As measured by the levulose[21] and galactose[19] tolerance tests, glycogenetic function is lowered. Changes in the blood lipoids[11] and serum proteins[12] and increased hemoglobin catabolism with bilirubin formation may also affect liver function. Clifford[1] has maintained that the liver is permanently damaged as a result of malarial infections.

Enlargement and slight tenderness of the liver are often present in naturally acquired malaria[18a] but has rarely been seen in therapeutic malaria. Clinical manifestations of liver involvement include icterus of a mild degree, bile-tinged vomitus, diarrhea, painful swelling of the liver, and dark-colored urine.[17] The liver is always enlarged and congested when death is due to malaria.[1] Histologic evidence of damage to the parenchymatous cells of the liver in fatal cases is not uniform, but both degenerative changes and fat infiltration are sometimes found.[14b] Cirrhosis of the liver is rarely seen. The duration of the primary disease and other concomitant circumstances play some part. Thus, malarial cirrhosis is frequent in southern Italy; whereas in other parts of the world and tropics it is rare.[17]

Icterus of the conjunctivæ occurs often im malaria, in 18 of 53 cases,[3] but it is not of serious import, both in our experience and that of others. The icterus has been attributed to the rapid destruction of the red blood cells, a hemolytic jaundice, and not to biliary obstruction. The icterus of the conjunctivæ may become more intense as the paroxysms recur only to disappear with continuation of fever. Jaundice of the skin, however, is considered a more serious and dangerous sign,[18b] and has necessitated immediate termination of the malaria. Jaundice is seldom seen during the first week or 10 days of the clinical attack, and is noted usually in patients in whom a high degree of parasitization of the red blood cells has produced a rapid and extreme anemia, 2 million or less, usually in 7 to 10 days.[22]

Malarial therapy has been administered in this clinic during the past 17 years to approximately 400 patients because of syphilitic

* This study was made possible by a grant from Merck & Co.

infections of the nervous system. Generalized jaundice has been occasionally seen but has rapidly cleared with the cessation of the malaria. In a recent study of the effects of long-continued administration of tryparsamide upon the liver, it was necessary to determine the effect of malaria *per se* upon liver function. In the present communication, we wish to report observations of the effect of malaria upon the liver function of 9 patients.

Material. Nine male patients, ranging in age from 32 to 55 years, were hospitalized for the malarial therapy of general paresis. Prior to malaria the physical and laboratory examinations revealed no significant pathology other than that of general paresis. Six of the patients had received no chemotherapy prior to malaria. The remaining 3 had received trivalent and pentavalent arsenicals.

Methods. The patient was inoculated with tertian malaria. After an incubation period ranging from 3 to 7 days, fever resulted and was usually of the quotidian or mixed type. The patients were allowed from 4 to 12 paroxysms. The malaria was then terminated by the administration of quinine sulphate, 30 gr. daily, for 1 week. During the malaria treatment, attempts were made to maintain the nutrition of the patients though food intake was in some instances voluntarily reduced. Following malaria, the patient was placed on a high caloric and vitamin diet and ferrous sulphate, 20 gr. daily.

Liver function was determined before and after malarial therapy by the following procedures: 1, bromsulphthalein dye test; 2, cholesterol, total, free, and ester; 3, phospholipids; 4, hippuric acid excretion; 5, cephalin cholesterol flocculation test of Hanger; 6, fibrinogen; 7, total bilirubin; 8, van den Bergh reaction; 9, icteric index.

The bromsulphthalein dye test was at first fractionated, 2, 5, 15 and 30 minute samples being taken following the injection of 2 mg. of the dye per kilogram of body weight. Subsequently, only 18 and 30 minute samples were obtained since MacDonald[13] has shown that 18 and not 30 minutes are required for complete removal of the dye in normal cases. The bromsulphthalein dye test is generally recognized as the most delicate index for the presence of liver disease in the absence of jaundice. Variations in hydration and kidney diseases do not affect the test. Congestive heart failure, however, makes the results unreliable.

Total cholesterol was determined on serum by a modification of the method of Bloor[2a] and the free and ester cholesterols by a modification of the technique of Schoenheimer and Sperry.[20] Total cholesterol values of 150 to 230 mg. per 100 cc., a free percentage of 23% to 31%, and an ester percentage of 69% to 77% were considered normal. A fall in cholesterol ester percentage is usually considered a serious sign and is found only in the presence of infection or liver disease.[24a] High ester values indicate a mild disturbance. Cholesterol metabolism may not be disturbed in the presence of considerable liver injury. Normal findings, therefore, do not rule out liver disease.

Phospholipid determinations were done on plasma following the lipid extraction technique of Bloor[2b] and the digestion method and phosphate determination of Fiske and Subbarow.[8] The normal range is from 8 to 9 mg. per 100 cc. Moderately reduced phospholipid values occur during the course of acute hepatitis.[24b] Increased values, from 14 to 27 mg. per 100 cc. have been found during acute infections and toxic hepatitis (arsenic, etc.).

Hippuric acid excretion was determined by the Weichselbaum-Probstein[23] modification of the technique of Quick. An excretion of 4 gm. or more

over a 4 hour period following the oral ingestion of 5.9 gm. of sodium benzoate was considered normal. The hippuric acid excretion test is positive in all types of liver disease.[24a] It can usually be correlated with the extent of liver damage, though normal findings may be obtained when liver damage is mild. The test is somewhat more reliable than the cholesterol ester percentage in the prognosis of cases of acute liver disease and far more reliable in the chronic cases of cirrhosis. It is helpful in prognosis since it invariably gives low results in severe and fatal cases. The hippuric acid excretion is altered in marked diminution of renal function.[16] The test was considered significant in our patients only when normal kidney function by dye excretion was present.

The cephalin-cholesterol flocculation test was carried out according to the technique of Hanger.[10] The cephalin-cholesterol antigen, dehydrated, was supplied by the Difco Laboratories, Detroit, Mich. The test was performed on freshly drawn blood serum and a control test was run on normal serum on every occasion. Readings were made at the end of 24 and 48 hours, no test being considered negative until 48 hours had elapsed.

Cephalin cholesterol emulsions are not usually flocculated by normal human serum, nor by serum from patients with obstructive jaundice.[10] They are unaffected by the red cell sedimentation rate or by the Wassermann reaction. A negative flocculation has also been obtained on patients with hemolytic jaundice. Cephalin cholesterol emulsions are flocculated by serum from patients with active disturbances of liver parenchyma.[10] The test serves as a means of distinguishing obstructive from hepatogenous jaundice. It does not parallel other liver function tests. Hanger has stated that the test is a more sensitive and accurate index of active disturbance of liver parenchyma than any of the liver function tests.

Fibrinogen was determined by precipitation as fibrin by the method of Cullen and Van Slyke,[5] and the nitrogen content of the fibrin determined directly. Potassium oxalate, 2 mg. per 100 cc. was used as the anticoagulant. The usual limits of normal are from 190 to 330 mg. per 100 cc.[9] Moderate liver damage itself is a stimulus to fibrinogen production. With more extensive destruction of the liver a failure of fibrinogen response occurs.

Bilirubin was determined by a modification of the van den Bergh technique.[16] Values of 0.8 mg. per 100 cc. or less were considered normal.

Results. Liver function tests before malaria were essentially normal in 8 of the 9 patients, except for the following: 4 patients showed slight bromsulphthalein retention (5% to 10%) at 18 minutes; and 5 patients revealed high fibrinogen values, from 340 to 540 mg. per 100 cc. These findings are not uncommon in patients with neurosyphilis prior to any type of therapy. Six of the 8 patients coöperated for the hippuric acid excretion tests which were normal. The ninth patient (J. T.), who had received intensive arsenical treatment over a 14-year period and had experienced a toxic hepatitis due to arsenic in 1928, revealed abnormal liver function tests; bromsulphthalein retention of 25% at 18 minutes and 10% at 30 minutes; lowered phospholipid values of 7.3 mg. per 100 cc. and a diminished hippuric acid excretion of 2.7 gm. (Table 1).

The administration of malaria causes marked changes in liver function as revealed by moderate bromsulphthalein retention, a marked fall in total cholesterol and cholesterol ester values, diminished hippuric acid excretion, and a strongly positive cephalin flocculation test (Tables 1 and 2). The degree of liver function impair-

TABLE 1.—EFFECT OF ADMINISTRATION OF MALARIA ON LIVER FUNCTION TESTS

Minutes | Cholesterol. | Hippuric | Fibrino- | Phospho-

TABLE 1.—EFFECT OF ADMINISTRATION OF MALARIA ON LIVER FUNCTION TESTS

Name. Age.	Date.	Wt.	Minutes 2-5-15-18-30 Bromsulphalein retention.	Cholesterol. Total mg. %.	Cholesterol. Ester, %.	Cephalin flocculation.	Hippuric acid excretion, gm.	Fibrinogen, mg. per 100 cc.	Phospholipids, mg. per 100 cc.	Bilirubin.	Van den Bergh.	Icteric index.	Hours fever above 100° (R).	Paroxysms.	Trypansamide, gm.	Malaria.
J. B.	12-15-41	163	5-0	200	66	0	5.65	390	8.2	Normal	Indirect	6				12-16-41 to
44	1-2-42	155	10-0	128	61	+++	5.04	280	7.6	Normal	Indirect	6	132	7		1-9-42
	1-22-42	153	10-0	162	69	+	4.58	330	8.0	Normal	Indirect	6	179	11		
	3-3-42					±						5			1¼	
A. C.	10-16-41	105	80-60- 5- 0-0	283	72	0		340	9.1	Normal	Indirect	5				5 typhoid vac-
55	11-10-41	111	100-80-15-10-0	284	67	+++		390	9.3	Normal	Indirect	5	23		1½	cine fevers,
	12-1-41	105½	10-0	203	55	++++		410	9.4	Normal	Indirect	4	112	9		10-27 to
	12-30-41	110	5-0	244	67	+		510	10.6	Normal	Indirect	5			+3½	11-5-41
	1-13-42					±									+8	11-7 to
																11-27-41
W. D.	9-5-41	157	100-80-15- 8-0	166	70	0	5.75	290	8.4	Normal	Indirect	4				9-9 to
51	10-6-41	142	100-80- -10-0	188	66	+++	5.04	270	8.3	Normal	Indirect	4	160	11		10-1-41
	10-21-41	163½	5-0	234	70	++	5.55	300	8.9	Normal	Indirect	5			1½	
A. E.	9-5-41	146½	80-35- 4- 0-0	163	71	0	4.87	350	8.1	Normal	Indirect	6				9-18 to
32	10-2-41	142	80-60-15-10-0	119	31	++++	3.05	260	7.5	1 mg.	Indirect	9	132	8		9-29-41
	10-9-41	144	100-80-30-25-10	207	63	+++	2.97	350	8.0	Normal	Indirect	6			½	
	10-23-41	145	90-55- 5- 0-0	204	66	+	4.58	320	8.1	Normal	Indirect	8			+3	
	1-15-42	155½	0-0	206	69	±	4.52	290	9.4	Normal	Indirect	5			+23	
	2-10-42					0									+9	
T. F.	9-15-41	185	80-50- 8- 5-0	211	73	0	5.60	320	8.1	Normal	Indirect	3				9-22 to
39	10-15-41	176½	10-0	116	60	+++	1.45	350	7.9	Normal	Indirect	6	139	11		10-16-41
	10-27-41	181	90-60-12- 8-0	183	68	++	3.51	260	9.3	Normal	Indirect	3				
	11-24-41	199	0-0	178	69	0	4.77	270	8.7	Normal	Indirect	4			5	
M. G.	2-9-42	146	0-0	210	74	0	4.23	250	8.6	Normal	Indirect	5				2-9 to
32	2-17-42					0							86	3		3-5-41
	2-19-42					0							95	4		
	3-2-42	133¼	5-0	70	10	+++		310	6.9	Normal	Indirect	6	159	11		
	3-5-42			76	30	+++	3.12			Normal	Indirect	5	164	12		
G. T.	1-22-41	151½	0-0	258	72	0	5.64	540	8.6	Normal	Indirect	6				1-20 to
39	1-27-41					0							40	2		2-9-42
	1-29-41					0							72	3		
	2-4-41	145¼				+++	5.3						103	6		
	2-13-41		5-0	111	50	±		290	7.8	Normal	Indirect	6	135	10		
	2-17-41					±				Normal	Indirect					
	3-2-41	140½	0-0	207	71	0		620	8.0			4				
J. T.	9-10-41	134½	90-60-30-25-10	222	74	0	1.80	310	7.3	Normal	Indirect	7				9-25 to
55	10-14-41	125	Jaundice	102	35	++++	1.50	300	7.0	2.4 mg.	Biphasic	15	110	7		10-13-41
	10-27-41	126	100-80-20-15-5	214	71	+	1.48	280	8.1	Normal	Indirect	7				
	11-24-41	136½	10-0	191	69	0	2.78	250	8.4	Normal	Indirect	6			3½	
	12-22-41	141	0-0	268	74	0		280	9.6	Normal	Indirect	6			+8	
	1-13-42			220	69					Normal	Indirect	6			+8	
H. Y.	11-21-41	137½	0-0	205	73	0		470	8.7	Normal	Indirect	5				11-26 to
53	12-10-41	124½	15-5	160	57	++++		260	7.2	1 mg.	Indirect	8	73	4		12-5-41
	12-30-41	124	4-0	187	65	0		430	9.2	Normal	Indirect	6				
	1-14-42					0									1	

ment did not appear to depend on the number of paroxysms, the total number of hours of fever above 100° (R), or the duration of active malaria. One patient (W. D.), aged 51 years, experienced 11 paroxysms and a total of 160 hours of fever above 100° (R) over a 19 day period. The liver function tests following the termination of the malaria were practically unchanged except for a +++ cephalin flocculation. On the other hand, a second patient (M. G.), aged 32 years, who experienced a similar number of paroxysms and fever over a 17 day period, showed marked changes in the liver function tests, a marked drop in the total cholesterol and cholesterol ester values, moderate bromsulphthalein retention, reduced hippuric acid excretion, lowered phospholipid values, and a +++ cephalin flocculation test (Table 1).

TABLE 2.—EFFECT OF MALARIA UPON LIVER FUNCTION.

	Normal range.	Before malaria.*	After malaria.
Bromsulphalein retention:			
18 minutes, %	0	3.5	9.4
30 minutes, %	0	0	0
Fibrinogen, mg.	190–330	367.8	303.3
Cholesterol:			
Total mg. per 100 cc.	140–230	219	126
Free, %	69–77	71.1	47.2
Cephalin flocculation	0	0	+++
Phospholipids, mg.	8–9	8.25	7.53
Hippuric acid secretion, gm.	4–6	4.9	3.5

* Based on average values of 8 patients.
Patient who developed jaundice omitted.

Each of the 9 patients showed a strongly positive cephalin flocculation test as a result of malaria. In 1 of the group (patient A. C.), a negative flocculation test was present before fever therapy, became +++ positive after 5 mild fevers induced by typhoid vaccine and ++++ after malaria. Each patient also experienced a fall in the cholesterol ester percentage. Initial ester percentages before malaria were normal and ranged from 66% to 74%. Values obtained after malaria ranged from 10% to 66% and were abnormal in 8 patients. Total cholesterol values showed a marked reduction from an initial range of 163 to 284 mg. to levels of 70 to 203 mg. In 1 instance (M. G.), the total cholesterol fell from 210 to 70 mg.

Hippuric acid excretion was examined in 7 of the 9 patients following malaria; in each a reduction occurred, and in 3 of the 7 the results were below normal levels. In a fourth patient (J. T.), hippuric acid excretion, below normal before malaria, was still further reduced.

Bromsulphthalein retention of a moderate degree and greater than that present before fever occurred in 6 of the 9 patients. Phospholipid values decreased only slightly in 8 patients. Fibrinogen was increased in 3 patients and diminished in 6, but remained within normal limits in the latter group.

Patient J. T. (Table 1), who had presented evidence of impaired liver function prior to malaria, developed generalized jaundice after 7 paroxysms and the malaria was terminated. A marked fall in total cholesterol and cholesterol esters occurred. The cephalin flocculation test became ++++ positive.

The termination of malaria by quinine was followed by a rapid return of the liver function tests to normal in 3 to 6 weeks' time with the exception of the fibrinogen and cephalin flocculation tests. In 3 of 8 patients, fibrinogen remained increased. The cephalin flocculation test was the last as a rule to revert to normal. The test became negative in 2 patients (H. Y. and G. T.) 21 and 25 days after quinine therapy was started. Tryparsamide, from 0.5 to 36 gm., had been administered to the remaining 7 patients, and the cephalin flocculation test in this group required as long as 19 weeks to return to normal. Liver function tests returned to normal levels fairly rapidly even in the patient who had developed jaundice (J. T.) and to whom tryparsamide had also been given.

Liver function tests, except for the cephalin flocculation, were obtained only after malarial therapy on a second group of 5 patients, and 2 to 9 days after the administration of quinine. The findings were as follows: 3 patients revealed normal liver function tests with the exception of an increased fibrinogen in 1. Of the remaining 2 patients, 1 developed jaundice and revealed the following 2 days after malaria was terminated: an icteric index of 15, bilirubin, 2 mg. per 100 cc., a biphasic van den Bergh, bromsulphthalein retention of 15% at 15 minutes, cholesterol esters 52%, and a moderately diminished hippuric acid excretion. The fifth patient, nine days after quinine, revealed diminished phospholipid values and a significantly diminished hippuric acid excretion.

Discussion. Malarial therapy produces disturbances in liver function which are, however, of a transient nature. The outstanding findings on our patients were the marked reduction in total cholesterol and cholesterol ester percentages, the fall in hippuric acid excretion and the strongly positive cephalin flocculation tests. Less marked were the phospholipid reduction, bromsulphthalein retention and the quantitative and qualitative bilirubin changes.

The findings obtained on patient J. T., who developed generalized jaundice during malarial therapy, indicate that the jaundice of malaria is due to liver damage. The presence of liver pathology in this patient prior to the administration of malaria and probably as a result of prolonged arsenical therapy and a previous toxic hepatitis may be an important factor. A second patient (A. E.), who revealed nearly similar abnormal function tests as a result of malaria, experienced no jaundice. Liver function in this patient prior to malaria was, however, normal.

The findings of impaired liver function in 3 patients during malarial fever and before quinine therapy would indicate that this drug

per se was not a responsible factor. This conclusion is strengthened by the fact that improvement in liver function occurred even during the administration of quinine. The rapidly induced hemolytic anemia of malaria resulting in excessive bilirubin production does not impair liver function since it has been shown that intravascular hemolysis of red blood cells as produced by autohemolysins does not result in abnormal liver function tests.[6] Liver function also is not impaired in the presence of a secondary anemia as occurs in malaria.[6]

Recently it has been shown that impairment of liver function occurs in protein-depleted animals.[7] The production of hypoalbuminemia by restriction of food intake in animals produced an increasing fall in protein content of the liver and histologic changes such as loss of stainable cytoplasm. Rapid and progressive hypoalbuminemia has been observed in malaria.[12] It is possible that impairment of liver function in malaria may be due to the marked reduction in the serum albumin with depletion of the proteins in the liver. Termination of the malaria causes a rise in serum albumin to its pre-febrile level, usually within 10 to 24 days. Normal liver function tests were obtained on our patients after malaria at a time when serum albumin is rapidly returning to normal levels.

Of some interest in the treatment of neurosyphilis is the occasional appearance of jaundice after malarial fever is terminated and following the administration of the first few injections of an arsenical. It is possible that the administration of arsenicals after malaria and before liver function has returned to normal may overburden the liver and result in jaundice. The danger is probably less with pentavalent arsenicals (tryparsamide), little of which is found in the liver after administration than with trivalent arsenicals (neoarsphenamine, mapharsen, arsphenamine), a considerable portion of which is excreted by the liver.

Summary. 1. Tertian malaria was administered to 9 male patients for the treatment of general paresis and liver function determined before and after therapy.

2. Malaria produces disturbances in liver function as revealed by moderate bromsulphthalein retention, a marked reduction in cholesterol and cholesterol esters, a moderate fall in the phospholipids, diminished hippuric acid excretion and a strongly positive cephalin flocculation test.

3. The impairment of liver function is transient and clears usually within 3 to 6 weeks after termination of the malaria. The cephalin flocculation test is the last to revert to normal.

4. The administration of pentavalent arsenic in the form of tryparsamide immediately after malaria did not seem to delay the return of liver function tests to normal with the exception of the cephalin flocculation.

5. The occasional appearance of jaundice after malaria has been terminated and following the administration of the first few injec-

tions of an arsenical may be due to the residual hepatic damage of the former and the superimposed toxic effect of the drug.

The technical procedures were carried out by Miss Mabel Miller.

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CLINICAL EXPERIENCE WITH A WATER SOLUBLE VITAMIN K-LIKE SUBSTANCE

(Tetrasodium 2-Methyl-1, 4-Naphthohydroquinone Diphosphoric Acid Ester)*†

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Although it has been almost 15 years since Dam[5,6,7,8] began his classic experiments leading to the discovery of the fat soluble vitamin K, the clinical progress made with this important substance and its derivatives had been quite slow until 1939, when it was

* Synkayvite "Roche."

† This work was aided by grants from the Douglas Smith Foundation for Medical Research, and Hoffmann-La Roche, Inc., Nutley, N. J.

shown that the activity of this vitamin was dependent upon its quinoid structure.[13] Many quinone derivatives were then studied for their antihemorrhagic activity, 2-methyl-1, 4-naphthoquinone being the first to be investigated in man. However this quinone and many of the others similarly studied are only very slightly soluble in water but freely soluble in most fat solvents. Therefore when orally administered, bile salts must of necessity be concomitantly given, or the preparation must be administered intramuscularly in oil. Thus its adaptability for general clinical use is limited.

The need for a water soluble vitamin K preparation suitable for oral, intramuscular or intravenous use has resulted in the synthesis of several compounds suitable for such purposes. Among the latter is the tetrasodium salt of the diphosphoric acid ester of 2-methyl-1, 4-naphthohydroquinone (Synkayvite), which has been found to possess an antihemorrhagic activity even greater than the fat soluble menadione (2-methyl-1, 4-naphthoquinone) when compared on an equimolecular basis.[4,9,11]

It is the purpose of this report to present data obtained on patients with hypoprothrombinemia to whom vitamin K therapy in the form of water soluble Synkayvite was given, and to demonstrate the wide margin of therapeutic safety this preparation possesses. In each instance the prothrombin content of the plasma was determined before therapy was instituted, and again after 24 hours and 72 hours had elapsed. The one-stage dilution technique previously described[3] was employed throughout. With this procedure a prothrombin level of 100% is considered normal.

Method. Forty-eight patients with prothrombin deficiency were studied, 31 of whom had a lowered prothrombin level due to inadequate absorption of vitamin K from the intestinal tract. The remaining 17 patients exhibited various conditions with a lowered prothrombin level of intrahepatic origin. Synkayvite was given orally to 29 patients, intramuscularly to 14 and intravenously to 5. In each case the daily dose and the initial and post-administrative prothrombin levels are given in the accompanying table (Table 1). Cases 14, 32 and 40 were more than usually interesting and are presented below in some detail.

Case Reports. CASE 14. Female, aged 35, was hospitalized with a diagnosis of postoperative common duct stricture. Jaundice of an obstructive origin had been present for 5 weeks. Bleeding from the gums and vagina had been noted for 10 days before admission.

When first determined the plasma prothrombin level was reported as 18%. Twenty mg. of Synkayvite were given intravenously each day and despite deep jaundice all evidence of hemorrhage disappeared within 4 hours of administration. Twenty-four hours after the Synkayvite was given the prothrombin level was 100%.

CASE 32. Male, aged 24, hospitalized for symptoms attributed to Banti's syndrome. On admission the plasma prothrombin level was reported as normal but fell to 75% after one month. At this time a daily dose of Synkayvite, 5 mg. by mouth was started. Within 24 hours the prothrombin level rose to 82% and at the end of 72 hours was 94%. In this case the response was most marked of all the patients suffering primarily from liver disease. It is likely that in this instance the involvement of the

liver was not so extensive as to preclude at least a partial response to the Synkayvite given.

CASE 40. Female, aged 23, admitted to the hospital with a diagnosis of acute myelogenous leukemia. An initial plasma prothrombin level of 58% was reported. Ten mg. of Synkayvite were given intramuscularly each day resulting in a rise to 60% of normal after 24 and 72 hours. However the patient expired 3 days after the last prothrombin determination had been made and it is probable that the failure of Synkayvite in this case was occasioned by the severe liver damage demonstrated at autopsy.

TABLE 1.—PROTHROMBIN BEFORE AND AFTER SYNKAYVITE

Case No.	Diagnosis	Prothrombin, % of normal			Daily dosage of tetrasodium 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester (Synkayvite), mg.	
		Initial	24 hours after treatment	72 hours after treatment		
1	Carc. of head of pancreas	43	100	100	5	orally
2	Common duct stone	85	100	100	5	"
3	Common duct stone	45	100	100	5	"
4	Carc. of head of pancreas	65	100	100	5	"
5	Carc. of head of pancreas	55	100	100	10	"
6	Carc. of stomach, no jaundice	82	100	100	10	intravenously
7	Carc. of common duct	58	100	100	10	orally
8	Common duct stone	55	100	100	10	intravenously
9	Ulcer. colitis, no jaundice	28	100	100	10	"
10	Carc. of stomach, no jaundice	55	100	100	10	"
11	Common duct stone	65	100	100	10	orally
12	Carc. of head of pancreas	48	100	100	10	"
13	Carc. of head of pancreas	62	100	100	5	"
14	Common duct stricture	18	100	100	20	intravenously
15	Compl. ext. biliary fistula	65	100	100	10	orally
16	Carc. of ampulla of Vater	83	100	100	5	"
17	Common duct stone	72	100	100	10	"
18	Common duct stricture	45	100	100	15	"
19	Carc. of head of pancreas	71	100	100	10	"
20	Carc. of esophagus, no jaundice	74	100	100	10	intramuscularly
21	Carc. of stomach, no jaundice	64	100	100	10	"
22	Ulcerative colitis	43	100	100	10	"
23	Common duct stone	58	100	100	10	orally
24	Common duct stone	86	100	100	5	"
25	Carc. of common duct	57	100	100	10	"
26	Common duct stone	39	100	100	15	"
27	Compl. ext. bile fistula	55	100	100	10	"
28	Carc. of ampulla of Vater	54	100	100	10	"
29	Common duct stone	45	100	100	10	"
30	Common duct stone	85	100	100	10	"
31	Carc. of common duct	65	100	100	10	"
32	Banti's syndrome, no jaundice	75	82	94	5	"
33	Cirrhosis, jaundice	60	68	85	5	"
34	Cirrhosis, jaundice	64	65	68	5 or 10	"
35	Multiple myeloma, large liver, no jaundice	63	63	62	10	"
36	Cirrhosis, no jaundice	75	80	83	10	"
37	Cirrhosis, jaundice	75	88	85	10	"
38	Cirrhosis, jaundice	70	70	70	10	intramuscularly
39	Cirrhosis	62	66	71	10	"
40	Leukemia, large liver	58	60	60	10	"
41	Leukemia, large liver	40	43	Expired	10	"
42	Cirrhosis, jaundice	71	70	70	10	"
43	Cirrhosis, no jaundice	80	80	83	10	"
44	Metastatic carcinoma of liver, jaundice	80	80	80	10	"
45	Cirrhosis, no jaundice	75	78	85	10	"
46	Acute catarrhal jaundice	63	68	79	10	"
47	Acute catarrhal jaundice	70	73	79	10	"
48	Abscess of liver	54	55	60	10	"

Therapeutic Safety. In order to determine the low toxicity of Synkayvite, 2 essentially normal individuals were chosen as experimental subjects. Both were adult males, aged 23 and 40 years respectively, and had been hospitalized for the repair of inguinal herniæ. Pre-experimental plasma prothrombin levels were normal and each subject was then given 200 mg. of Synkayvite intraven-

ously followed by the determination of daily prothrombin levels over a 7-day period. In no instance was there noted any untoward symptoms, alteration in prothrombin level, change in hematologic picture or urine. The results are summarized in Table 2.

TABLE 2.—BLOOD VALUES IN 2 NORMAL INDIVIDUALS

	Case 1		Case 2	
	Initial	At end of 7 days	Initial	At end of 7 days
R.B.C. (in millions)	4 8	5 1	5 1	5 2
Hb. (in grams)	16	16	16	15 5
W.B.C. (in thousands)	6 0	7 2	7 8	9 7
Prothrombin (%)	100	100	100	100

The blood smears were entirely normal, including differential count and character of leukocytes.

Comment. From Table 1 it will be noted that every patient (Cases 1 through 31) whose prothrombin deficiency was the result of a defective absorption of vitamin K responded rapidly; the prothrombin always returned to normal within 24 hours. The remaining 17 cases, whose prothrombin levels were not so dramatically changed, were without exception instances of intrinsic liver damage in which it is presumed the hepatic lesions were so extensive that the organ could not accelerate prothrombin production even though given an excess of the vitamin.

The vitamin K preparation employed gave satisfactory results in the patients who were subjected to major operative procedures, regardless of the route chosen for its administration. However, in general, it was noted that a more sustained effect was obtained when the oral or intramuscular route was chosen than when intravenous administration was instituted. In the latter case it seems not improbable that a greater amount of the active substance was excreted through the kidneys before its total effect could be obtained.

Recently, Allen and Julian[2] have emphasized the diagnostic importance of the effect of a trial dose of vitamin K in patients with jaundice and prothrombin deficiency. Patients whose hypoprothrombinemia results from inadequate absorption of the vitamin display a rapid return of prothrombin to normal within 8 to 24 hours. In those cases in which the prothrombin reduction results from primary liver disease little or no benefit from the use of the naphthoquinone is obtained. These two distinctly different responses to a trial dose of the vitamin serve as an excellent means for differentiating between intra- and extrahepatic jaundice. In applying this differential method a single dose of the vitamin is administered and the prothrombin again observed after 12 hours. In order to assure prompt response the naphthoquinone should be administered intravenously. For this purpose we have found the water soluble tetrasodium salt of 2-methyl-1, 4-naphthahydroquinone diphosphoric acid ester more advantageous than the fat soluble compounds which can only be used orally or intramuscularly in oil.

Toxic manifestations due to the administration of vitamin K or one of its preparations are apparently rare in animals or in man. Recently Molitor and Robinson[14] found that in mice the oral lethal dose was approximately 200 mg. per kg. of body weight for phthiocol and 500 mg. per kg. for 2-methyl-1, 4-naphthoquinone. However, no lethal effects were observed in doses up to 25 gm. per kg. in the case of natural vitamin K (2-methyl-3-phytyl-1, 4-naphthoquinone). Foster,[10] using Synkayvite, found that large doses must be given before a lethal effect is noted (450 mg. per kg. in the case of mice in which the drug was given intravenously or subcutaneously). Toxicity was observed in rabbits when 50 to 200 mg. per kg. were given. Such symptoms included an acceleration in the respiratory rate, rise in temperature, pin-point pupils and a state of anxiety and apprehension. Shimkin[16] states that transitory mild collapse and respiratory embarrassment appeared early, that later the legs extended, the animal became cyanotic, the urine brown in color, and that death was the result of respiratory failure.

Experiments conducted by Foster, Smith and Ivy[12] in which large doses of Synkayvite were given over an extended period of time showed that a slight loss in weight was noted in rats fed 10 doses of 100 mg. per kg. over a 14 day period. Rabbits receiving similar doses over a 20 day period displayed a mild anemia while larger doses produced a marked aplastic anemia with a 50% mortality. These investigators also noted a yellowish-brown or pinkish-orange discoloration of the fur of rats and rabbits subjected to repeated high dosage of this drug. However no local irritation was found.

Allen[1] has reported on the daily administration of 8 mg. of menadione (2-methyl-1, 4-naphthoquinone) to a human patient over a period of 18 months. No toxic or untoward effects have been noted. This patient has continued receiving the same daily dose now for 30 months, still without any signs of toxicity. It would seem therefore that the toxic dose of the naphthoquinones apparently so greatly exceeds the therapeutic dose that there is little risk of any toxic reactions when the drug is administered in the routine treatment of the patient.

The results obtained in the present experiments indicate that the acutely toxic dose of Synkayvite seemingly is far greater than the advised therapeutic one.

Summary. 1. The tetrasodium salt of 2-methyl-1, 4-napthohydroquinone diphosphoric acid ester, a water soluble vitamin K-like substance, was administered to 31 patients with obstructive jaundice and 17 with intrahepatic jaundice. This drug uniformly elevated the prothrombin in the obstructive jaundiced patients. In those patients with intrahepatic jaundice the prothrombin response was comparatively slight.

2. No toxic symptoms were noted during the course of clinical

trial with this substance, even though a single dose of as much as 200 mg. was administered in two instances. The coagulation time was not abnormally shortened.

3. This new water soluble naphthohydroquinone is especially valuable in the postoperative care of the jaundiced patient. Such patients frequently display a reduction of prothrombin a day or two after operation even though preoperative therapy was carried out. This postoperative hypoprothrombinemia can be prevented or corrected by the parenteral administration of a water soluble preparation.

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THE WATER AND ELECTROLYTE DISTRIBUTION IN DIABETES MELLITUS*

Dehydration in Diabetes

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Our present knowledge of the pathologic physiology of diabetes is due largely to the application of chemical methods to the problems presented by the patient. At the beginning of this century internal medicine had developed to a point where chemical help was indispensable in the diagnosis and treatment of the patient—especially the diabetic patient. Out of this need was developed the present clinical chemistry division of the hospital laboratory.

* Read before the Cincinnati Academy of Medicine on "Diabetic Day," March 3, 1942.

Initially, this branch of chemistry utilized the older, cumbersome methods of quantitative chemical analysis, but it soon became necessary to develop new procedures. Thus, it is questionable whether the use of insulin, or perhaps even its discovery, could have been possible without the timely improvements in the methods of analysis for blood sugar. The best methods of analyzing for sugar 50 years ago required from 100 to 500 ml. of blood and time-consuming analytical work. The development of micro-methods for blood sugar analysis, first by Bang in 1913,[2] however, made it possible to make analyses upon 1 ml. or less of blood within a half hour. Thus, one might ask what might be the present status of our knowledge of diabetes were it not for this great advance in methodology. In a real sense, the application of chemical methods has been the cement which has bound together the foundations of our knowledge of diabetes.

In no disease has the composition and character of the body fluids and tissues been more intensively studied than in diabetes mellitus. This applies especially to its most serious complication—diabetic acidosis. Important advances have been made in recent years in our knowledge of the distribution of the salts of the body under various normal and pathologic conditions. Gradually insight has been gained into the disturbances produced by alterations in the distribution of salts. We wish to direct attention particularly to these disturbances in diabetes mellitus. In this field of metabolic research we are especially indebted to the contributions of Gamble and his associates[5,6] on dehydration and the mass movement of salt and water in the body; to the serum electrolyte studies of Peters,[8] Peters and Van Slyke,[9] of Guest and Rapoport[7] and of others; and to the electrolyte balance studies in diabetic acidosis by Atchley, Loeb and their co-workers.[1]

Our approach to the distribution of water and electrolytes in diabetes mellitus has consisted in the main of 3 types of study: (1) changes produced by the administration of glucose to diabetic patients without ketosis;[13] (2) changes produced by the injection of insulin to severe diabetic patients;[10] (3) changes observed in depancreatized dogs permitted to lapse into diabetic ketosis.[12]

The first study was designed to determine in the diabetic patient to whom glucose was administered the changes in activity of glucose and chloride in the serum as well as changes in the total content of these components.

The experimental procedure was essentially as follows: Blood serum was obtained after an overnight fast from severe diabetic patients to whom the administration of insulin was temporarily stopped. Seventy-five grams of glucose were administered to each patient and after an interval of 90 minutes, serum was again obtained.

In these studies special conditions existed such that without

direct measurement of serum volume one may draw reasonably reliable inference as to changes in the total amount of the serum components in the body. Assuming that the solids of the serum (which are between 90 and 95% protein) remain constant during the 90-minute period of the experiment (and for our purposes this assumption is acceptable), then the concentrations of the components may be expressed in relation to the solids and the percentage change in the total amount of these components may be calculated. In Table 1 are given data taken from a typical case.

TABLE 1.—EFFECT OF INGESTION OF GLUCOSE (CASE 6)

Serum	Before glucose	After glucose	Difference
Specific gravity	1.0291	1.0289	
Solids, gm. kg. serum	93.95	87.10	−6.85
Cl, mEq. liter serum	100.1	98.2	−1.9
mEq. kg. serum water	107.4	104.5	−2.9
mEq. kg. serum solids excl. glucose and Cl	1121.2	1221.1	+99.9
Glucose, mM. liter serum	8.5	19.4	+10.9
mM. kg. serum water	9.1	20.7	+11.6
mM. kg. serum solids excl. glucose and Cl	94.7	264.8	+170.1
Water, gm. liter serum	932.4	939.3	+6.9
gm. kg. serum solids excl. glucose and Cl	10441.0	11686.0	+1245.0

The concentrations of glucose and chloride before and after the administration of glucose have been expressed in relation to the water and solid concentration in the serum. It will be observed that there was an increase in the total amount of glucose (mM. kilo serum solids) as well as an increase in its concentration in the serum (mM./liter serum). Although the concentration of chloride decreased, the total amount of chloride in the serum increased. The total amount of water in the serum increased following the ingestion of glucose.

From such analyses it has been possible to calculate the percentile increase in the water of the serum and also the molal concentration of the added glucose and added chloride calculated as if it were in this added water. The percentile increases in the water of the serum after the ingestion of glucose, are shown in the upper portion of Chart 1. Our analyses require that the solution transferred to the serum with the glucose contain from 0 to 103 mEq. of chloride per kilogram of water. The addition of glucose to this saline solution usually gave a solution for which the calculated molal concentration was higher than for the fasting serum. This calculation was corroborated by an observed slight increase in the freezing-point depression in the serum obtained after glucose ingestion. In the upper portion of Chart 1 are given also the results obtained following the ingestion of glucose in 2 normal individuals. In these 2 individuals there was an outflow of water as well as of glucose and chloride. The changes in the controls are the reverse of those observed in the diabetic patients.

In Chart 2 is plotted the increase in the milliosmolal concentration of glucose in the serum against the decrease in the milliosmolal concentration of chloride. The statistically calculated regression line is: $-\Delta\pi Cl = 0.369\Delta\pi$ glucose $+ 1.50$. If the milliosmolal decrease in the concentration of chloride were equal to the millios-

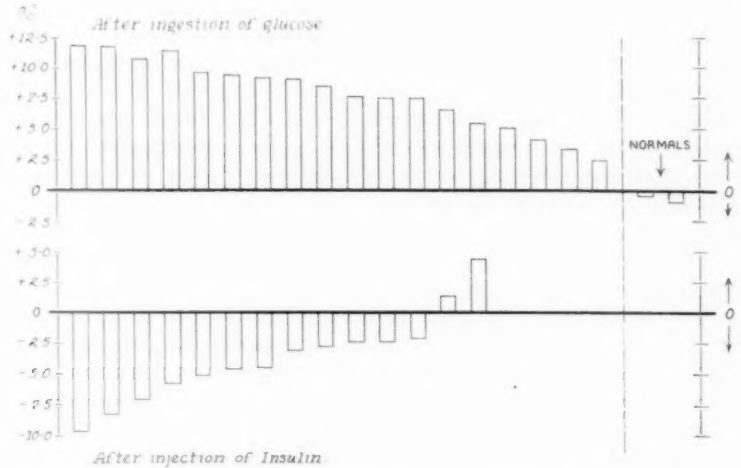

CHART 1.—Percentile change of water content in serum of diabetic patients.

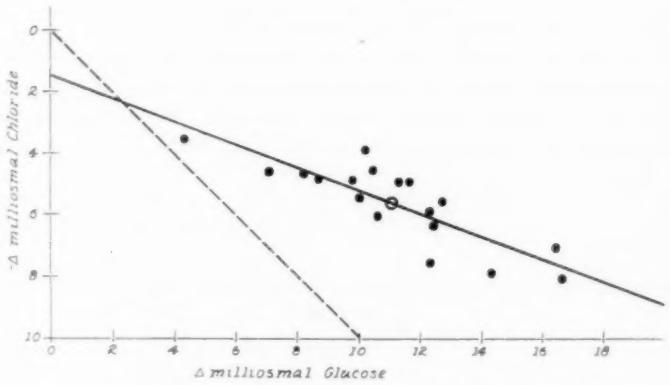

CHART 2.—Increase in osmolal concentration of glucose against decrease in osmolal concentration of chloride.

molal increase in glucose, the data would follow the dotted line. Increase in the concentration of glucose is thus not entirely compensated for osmotically by decrease in the concentration of chloride.

The simplest schematic interpretation of the situation here portrayed is that the uptake of glucose in the serum of diabetic patients

(but not in normal individuals) tends to draw water into the serum from the tissues. The water added to the serum with the glucose tends to dilute the serum electrolytes, and to set up a potential gradient for electrolyte from tissue to serum, hence an inflow of chloride into the serum. Thus in the diabetic patient a potential gradient induced with respect to glucose, induces secondarily a potential gradient with respect to electrolyte. The diuresis that usually ensues following the ingestion of glucose in diabetic patients may be a reflection of the increased content of water poured into the serum.

A second approach to the problem of the distribution of electrolytes in diabetic patients was made by determining the changes induced in the serum following the administration of large doses of insulin to diabetic patients with high blood sugars.

After a period without insulin long enough to induce marked elevation of blood sugar and after an overnight fast, sufficient blood was withdrawn for a complete analysis of the electrolytes. The patients were then given a large dose of insulin (50 to 120 units), still fasting. Following the insulin the patients were permitted to ingest water as desired. When the blood sugar had fallen to within normal limits (within 40 minutes to 3 hours), or upon the appearance of any symptoms of an insulin reaction, a second specimen of blood was removed and the study was discontinued.

In Table 2 are given data from a typical case. After insulin administration to the diabetic patients, the solids of the serum tended toward increased concentration. Assuming that the solids exclusive of glucose and chloride in the serum remain constant during the brief period of these observations, then the change in the total amounts of components in the circulating serum may be calculated. When such estimations are made, there can be demonstrated a decrease in the total amounts of glucose, chloride, and water in the serum.

TABLE 2.—EFFECT OF INSULIN (CASE 6)

Serum	Before insulin	After insulin	Difference
Specific gravity	1.0289	1.0292	
Solids, gm./kg. serum	88.70	93.50	+4.80
Cl, mEq./liter serum	96.1	99.4	+3.3
mEq./kg. serum water	102.5	106.5	+4.0
mEq./kg. serum solids excl. glucose and Cl	1174.8	1109.1	−65.7
Glucose, mM./liter serum	21.4	4.8	−16.6
mM./kg. serum water	22.8	5.2	−17.6
mM./kg. serum solids excl. glucose and Cl	261.6	53.9	−207.7
Water, gm./liter serum	937.6	933.0	−4.6
gm./kg. serum solids excl. glucose and Cl	11463.0	10420.0	−1043.0

In the lower portion of Chart 1 are shown the percentile decreases in the water of the serum after injection of insulin. This anhydremia which develops when insulin is given has long been recognized.

Following the administration of insulin to dogs, Drabkin, Page and Edwards,[3] and Drabkin[4] demonstrated that there was increased concentration of hemoglobin, increased erythrocyte counts and reduction in the plasma volume.

After the administration of insulin, the concentration of serum sugar was decreased in the serum in all of the diabetic patients. It is interesting to note, however, that in 4 of the observations the study had to be terminated at a time when the concentration of serum sugar was above 200 mg. per 100 ml. because of the appearance of insulin reactions. In these patients the shocklike reactions occurred when there had been a high initial blood sugar with fall in concentration of sugar amounting to 1 mg. or more per 100 ml. per minute. Neither high initial serum sugar nor rapid rate of fall independently induced reactions but the combination of these two factors did so. These shocklike reactions, which we could not distinguish clinically from the ordinary insulin reaction, developed while the serum sugar concentrations were still above 200 mg. per 100 ml. They were promptly relieved by the administration of glucose.

Before insulin administration the chloride concentration in the serum of the diabetic patients decreased below the normal range in 13 out of 17 observations. After insulin administration in each case the chloride concentration was increased above the original value, the increase after insulin amounting to as much as 7.6 mEq. per liter of serum. Similar relationships were observed with respect to the total base and sodium concentrations in serum (as with chloride). In the majority of cases the concentration of sodium and of total base were increased above the original values. As with the chloride measurements, it can be demonstrated that, although the concentration of these components was increased after insulin, nevertheless, the total amounts of total base and sodium in the circulating serum were decreased. The changes in the serum of diabetic patients following the injection of insulin were essentially the reverse of those observed when these patients received glucose without insulin.

The direction in which changes occurred in the distribution of glucose and chloride in the serum of severe diabetic patients without ketosis has been summarized in Table 3.

TABLE 3.—CHANGES OBSERVED IN THE SERUM OF DIABETIC PATIENTS

Serum	Concentration	Total amount
After Ingestion of Glucose		
Glucose	>	>
Chloride, total base (volume >)	<	>
After Injection of Insulin		
Glucose	<	<
Chloride, total base (volume <)	>	<

The third approach to the problem of the distribution of water and electrolytes was designed to determine, by direct methods, the changes in the concentration and in the total amount of components in the circulating serum during the ketosis of experimental diabetes induced in dogs by pancreatectomy. In addition to measuring the serum volume directly by means of dye injection, the amount of extracellular fluid was estimated by the NaCNS method.

Large healthy dogs were kept under constant conditions in their cages for a week or more before studies were made. After this preliminary period and a fasting period of 24 hours, the animals were given nembutal parenterally, following which measurement of serum volume was made by the vital red method[11] and blood was withdrawn for chemical analyses. Total pancreatectomy was then performed. After operation, the animals were given maintenance doses of insulin until recovery had occurred. After the operative scars had completely healed and the animals were regarded as in acceptably good condition, insulin therapy was completely withheld and the animals were permitted to go into ketosis. Final measurements were made when ketosis was well developed. The period of time required for the development of severe ketosis varied with individual dogs, some remaining active for as long as 3 weeks following the withdrawal of insulin. All of the animals had heavy ketonuria for several days before the final measurements were made, although some had relatively little fall in concentration of serum CO_2.

Since all of the depancreatized dogs lost greatly in body weight, the effect of ketosis following simple fasting was also studied in measurements on 2 dogs before and after losing a fourth of their body weight.

Since the changes in the individual serum constituents were all consistent in the depancreatized dogs we present only the average of the serum values obtained during the control period and during ketosis. The results of these analyses are given in Table 4.

TABLE 4.—AVERAGE OF SERUM ANALYSES (6 DIABETIC DOGS)

	Period	
	Control	Diabetic ketosis
Serum volume, ml./kg. body weight	52.8	70.3
Sugar, mg./100 ml.	106.0	450.0
Solids, gm./100	7.4	6.7
Protein, ml. gm./100	5.4	5.0
F.A., mM./L.	9.3	17.0
Cholesterol, mg./100 ml.	182.0	184.0
Total base, mEq./L.	147.8	139.8
Chloride CO_2:		
mEq./L.	109.4	101.5
Volume %	57.0	37.0
Undetermined anion, mEq./L.	3.8	13.4
$\triangle$, °C.	−0.545	−0.593
Urea N, mg./100 ml.	22.0	30.0

During the control period the average serum volume was 52.8 ml. per kilo of body weight; all of these measurements were within the normal range of values previously obtained on normal dogs in our laboratory. Following ketosis the serum volume per kilo of body weight increased in all of the dogs (averaging 70.3 ml. per kilo).

The concentration of sugar increased from the average value of 106 mg. per 100 ml. during the control period to 450 ml. during ketosis. The concentrations of serum solids and serum proteins decreased during ketosis. The concentration of fatty acids increased to approximately twice the normal value. Cholesterol estimations were made in 5 animals; 2 exhibited increased cholesterol concentrations during ketosis; 2, decreased concentrations; and 1 exhibited no change.

The concentrations of total base, Cl, and CO_2 decreased in the sera of all of the depancreatized dogs during ketosis. The concentration of undetermined anions was obtained by adding the values of BCl, $BHCO_3$ and BPr and subtracting this sum from the value for total base. In all but one of the dogs the concentrations of undetermined anions increased greatly during ketosis.

The freezing-point depression of the sera increased above the value obtained initially. The decrease in the osmolar concentrations of total base during ketosis was thus more than compensated by the increased osmolar concentration of sugar and other non-electrolytes. The concentration of urea increased during ketosis.

As all of the diabetic dogs suffered severe reductions in body weight, comparison of similar measurements was made in dogs subjected to simple fasting. The result of these measurements is not given in the table. However, with the exception of a slight reduction in the concentration of serum protein and cholesterol and a slight increase in the concentration of undetermined anion, the concentrations of serum components exhibited no essential change during fasting.

The amounts of components in the circulating serum were calculated during the control period and during ketosis and were compared in two ways. First, the total amount of a given component in the serum during ketosis was compared to the total amount of that component present during the control measurements. Second, the total amount of a given component *per kilo of body weight* during ketosis was compared to the total amount of that component per kilo of body weight during the control measurements. In Table 5 are given the average of the percentile changes in the amounts of serum components during ketosis as related (1) to the total amount present in the circulation during the control period, and (2) as related to the amount present per kilo of body weight during the control period. The values in the depancreatized animals are compared to those obtained in the fasted animal.

From the time of the initial to the final measurements the diabetic

dogs lost weight amounting from 25 to 43% (average, 33%). Final measurements were made in the fasted animals after a reduction of 26% of the body weight.

In Table 5 it will be seen that although the total amount of serum present in the circulation during ketosis was 10% less than in the healthy state, the serum volume per kilo of body weight was on the average, 29% greater than in the healthy state. In the fasted animals the total serum volume decreased in proportion to the reduction in body weight (24%) so that the serum volume per kilo of body weight remained constant.

TABLE 5.—PERCENTILE CHANGE IN SERUM CONTENTS DURING KETOSIS

	Diabetes		Fasting	
	Total	Per unit of body weight	Total	Per unit of body weight
Body weight	−33		−26	
Serum:				
Volume	−10	+29	−24	+2
Water	−0.8	+33	−24	+3
Total base	−15	+23	−26	0
Cl	−16	+25	−27	−2
BPr	−16	+20	−30	−7
$BHCO_3$	−45	−17	−36	0
Sugar	+282	+431	−31	−7
Cholesterol	+6	+49	−37	−16

In the diabetic dogs the total amount of water in the serum during ketosis was unchanged although the serum water per unit of body weight increased 33%. In the starved dog the total serum decreased in proportion to the decrease in body weight, so that the serum water per unit of body weight was unchanged. The total amounts of total base, Cl, and BPr in the diabetic dogs all decreased during ketosis, although the amounts of all of these components per unit of body weight increased. In the fasted animal the amounts of these components per kilo of body weight remained almost unchanged during ketosis.

Of all the serum components studied in the diabetic dog and expressed per unit of body weight, only the *bicarbonate content* per kilo of body weight was consistently decreased. These analyses of serum in the depancreatized animals are in marked contrast to those obtained during the ketosis of fasting. In the fasted animal the total amount of each of the serum components per unit of body weight as well as the serum volume per unit of body weight remained practically unchanged with the exception of protein and cholesterol which were decreased.

The results of the measurements of the extracellular water in two of the depancreatized dogs (E_2 and E_5) and of one fasted dog (E_6) are shown in Table 6. During ketosis in the depancreatized dogs, extracellular water per unit of body weight increased 12.5 and 8.4% respectively, while in the fasted animal the extracellular

water increased only 3.7%, which may be within our experimental error. In the diabetic animals the total amount of extracellular water present during ketosis was little if at all changed from that measured during the normal state in spite of loss of body weight.

TABLE 6.—EXTRACELLULAR WATER

Dog	Period	Body weight, kg.	Extracellular water	
			Kg.	% of body weight
E_2	Control	15.3	4.89	31.0
	Diabetic ketosis	11.3	4.89	43.5
E_5	Control	33.8	10.64	31.5
	Diabetic ketosis	25.5	10.16	39.9
E_6	Control	16.2	5.44	33.6
	Fasting	12.1	4.51	37.3

During the development of diabetic acidosis excessive amounts of water and electrolytes are excreted in the urine. Atchley, Loeb and their associates,[1] in balance studies of patients during the early stages of diabetic acidosis produced by the withdrawal of insulin, observed excretion of base greatly in excess of the amounts ingested. Most striking, perhaps, in their observations was the increased urinary excretion of intracellular constituents (K, PO_4, SO_4 and N) during the acidosis periods. In one of their patients the loss of potassium exceeded the loss of sodium. A question that obviously arises is: which space or spaces in the body supply the water and electrolytes that are excreted?

It is the usually accepted concept that dehydration is accompanied by a withdrawal of water from both the extra- and intracellular fluid compartments and that the serum volume falls when the interstitial fluids attain a certain minimal value. Support for this theory has been derived chiefly from Na and K losses from the body. However, our studies would indicate that during the dehydration of diabetic ketosis the water and electrolytes apparently do not come from the circulating serum, since the total amounts of these components may be increased. It would seem to us that, in the main, the extracellular fluid provides the Na and Cl for excretion; the cells supply the K, PO_4, SO_4, and N, and the intracellular space provides the water.

Chart 3 is our schematic representation of the electrolyte changes in the body during the course of diabetic acidosis. The first column represents the normal concentration of the electrolytes of the serum, the normal volume of serum and the normal amount of water and electrolyte in the extravascular spaces. During the development of diabetic acidosis, ketone acids (β-hydroxybutyric and diacetic acids) increase in excessive amounts. The increase in these acids displaces HCO_3^- which is expired into the air as CO_2. The kidneys tend to maintain a normal electrolyte pattern by excreting organic acids in the urine as free acids and in combination with NH_3^+. In this process the production of NH_3^+ is insufficient for combina-

tion with the organic acids awaiting excretion and as a consequence, fixed base is excreted for the purpose. This loss of base necessitates the withdrawal of water if isotonicity of the body fluids is to be maintained. Coincident with the withdrawal of base and water from the tissues, the serum volume and the total amounts of base and chloride in the serum increase. Increasing concentrations of glucose, urea and other non-electrolytes appearing in the serum

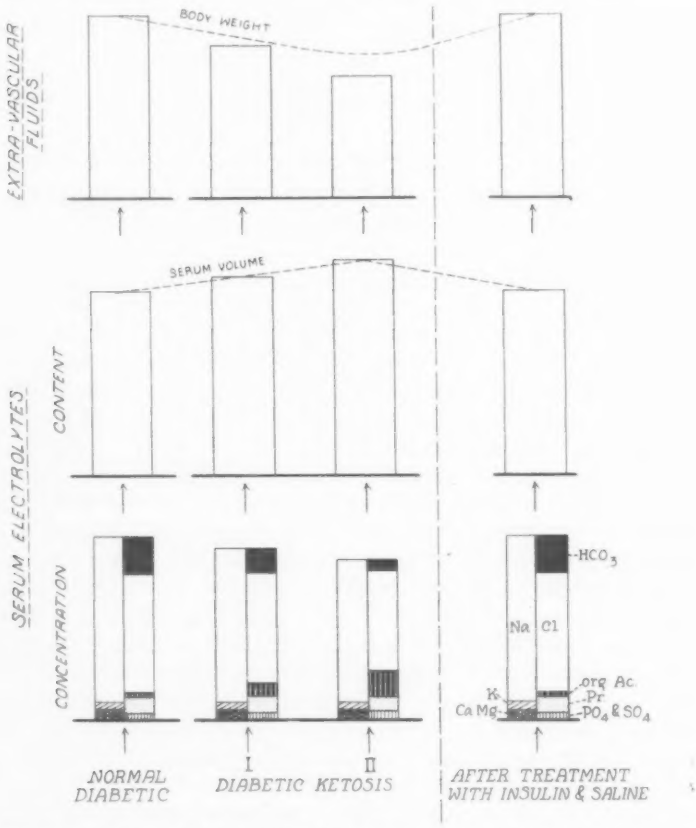

CHART 3.—Schema demonstrating changes in relation to diabetic ketosis.

elevate the total osmotic pressure of the serum. In partial compensation the concentration of the electrolytes may be decreased by increase of serum water, although the total amount of electrolyte is increased.

Finally, as shown in the third column, the extravascular fluids become greatly depleted and, with the continued demand for fixed base to combine with the organic acids, chloride begins to release its base by its secretion as HCl in the vomitus. The protoplasmic

structure of the organism is soon unable to withstand further strain, and unless therapy is instituted, death ensues. In the last column is shown a return to the normal distribution after administration of insulin and saline.

A most conspicuous feature in the development of diabetic acidosis leading to coma is the depletion of fixed base and water. Administration of saline solutions alone will not alleviate the resulting dehydration. However, the administration of *insulin* together with saline solutions results in transfer of water and electrolytes from the serum to the extravascular fluids and is recognized as the only successful method of combating the dehydration of diabetic ketosis. The action of insulin is followed by a decreased production of organic acids and, as a consequence, the electrolyte pattern and osmotic pressure of the serum gradually return to their normal values. Such, in outline, is the rôle played by the electrolytes during the course of diabetic coma.

The extreme dehydration occurring in diabetic ketosis is perhaps most strikingly shown by the gain in weight during convalescence. In one patient, recently studied, the gain in weight amounted to 8 pounds in 4 days.

The occurrence of coma in diabetic patients is precipitated by acute infections in more than 50% of the cases. During the early stages of such an infection the patient is often urged to drink copious quantities of water; or, because of the beginning of dehydration, he may possess a craving for water. This water, if unaccompanied by salt, cannot be stored and is excreted. In its excretion it tends to carry salt with it, thus further depleting the body's reserve of base. Therefore, the ingestion of water alone may hasten dehydration in the diabetic patient, whereas water given with the proper amount of salt is one of the simplest and most effective methods of forestalling dehydration. However, and above all, it must be emphasized that in providing for a return toward the normal distribution of water and electrolytes in the vascular and extravascular fluids of the diabetic patient with ketosis, *insulin*, in addition to saline solutions, is essential. No lasting significant beneficial effects will be secured when saline solutions are given diabetic patients in coma unless adequate amounts of insulin are also given with saline.

Summary. We have indicated the altered distributions of body water and electrolytes associated with diabetes. Administration of glucose to the severely diabetic individual without ketosis leads to a transfer into the circulating serum of water, NaCl, and glucose from the body tissues, so that the total amount of these components in the serum is increased, even though the concentrations of the electrolytes in the serum may actually be decreased. Likewise, in depancreatized dogs with ketosis there is a continued transfer of water, NaCl, and glucose from the tissues into the circulation. On the other hand, administration of insulin to the diabetic human

produces a reversal of these processes and causes transfer of water and electrolytes from the serum into the tissues. We wish to emphasize this action of insulin in readjusting the partition of water and electrolytes in diabetic individuals as important among its varied and complex effects.

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FAMILIAL CRETINISM

Two Brothers Exhibiting Thyroid Deficiency and Epiphyseal Dysgenesis

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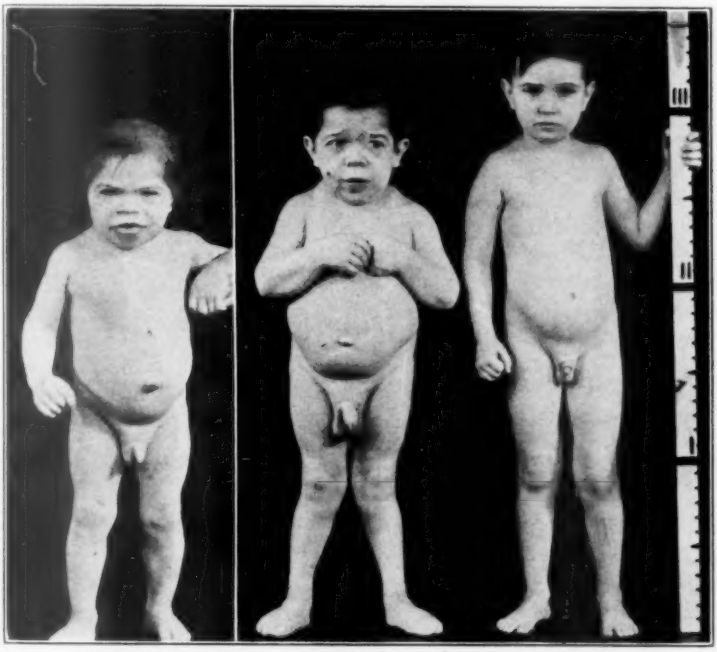
Familial cretinism is a rarity in this country. It is not uncommon where thyroid deficiency is endemic, as in Switzerland. In the review of the American literature, we were able to find but very few instances, and none quite similar to the one we are reporting.

Hosen[7] described hypothyroidism in twins. Reilly[12] reported a family with physical characteristics resembling hypothyroidism. Shelton[15] described 4 cases of hypothyroidism in one family in which the stature was under the accepted standards. Stevens[16] reported 4 cases which he categorized as sporadic cretinism; Goodkind and Higgins[4] mention the occurrence in 2 siblings. Watson[17] reported 3 cases in one family which he termed cretinoid amentia. Herrman[5] presented 2 different families with 3 cases of hypothyroidism.

Sanderson[14] reported 3 cases in one family which he termed sporadic cretinism. Ebright[3] and MacIlwaine[10] both reported cases of myxedema in pregnant women whose children developed cretinism following birth. Johannsen[8] reported a Scandinavian family in which he was fairly certain that 3 of the members were cretins. Familial cretinism or myxedema is discussed by Albrecht,[1] Laure and Patry,[9] Pighini,[11] Artom and Fornara,[2] but careful study of these articles fails to reveal a similarity to our patients.

Case Reports. CASE 1. E. D., a 13-year-old male, a typical sporadic cretin, entered the Cook County Hospital in February, 1940. He was admitted because of a prolapsed rectum which was reduced under surgical anesthesia. On questioning the parents about medical attention for this child it was found that none had been sought because of the presumable failure of medication on a previous sibling for a similar condition. This boy will be described subsequently.



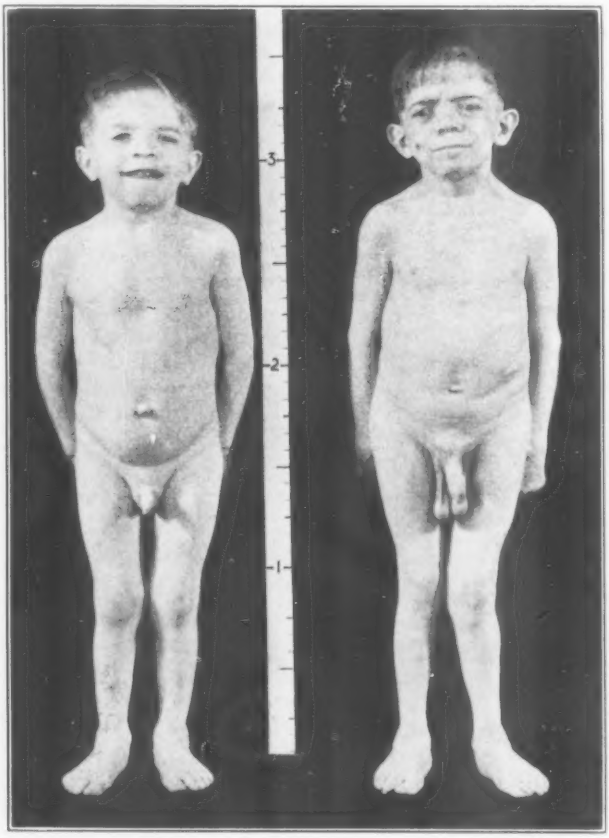
A *B* *C*

FIG. 1.—*A*, Cretin, aged 13 years. *B*, Brother, aged 23 years. *C*, Normal boy of 7 for comparison.

The family history is one of the interesting features of this report. Two of the mother's first cousins had thyroidectomies performed 10 years ago. The mother's sister, now a resident of German Poland, is reported to have an enlarged thyroid gland. The father and mother appear to have adequate physical and mental development. There are 7 children: the oldest, a girl of 24 years who had a thyroidectomy at the age of 21 years; 4 others who are apparently normal, and our patients.

At entrance, E. D. weighed 39½ pounds and was 36¼ inches tall (Fig. 1*A*). He spoke no syllables, carried out no simple commands, was unable to walk, and had the intelligence quotient of an 18-month-old infant. The dwarfed stature and mental inadequacy, in addition to supraclavicular fat pads, macroglossia, large abdomen and dry skin readily identified him.

Roentgenograms of the bones revealed marked retardation of skeletal growth, with fragmentation and stippling of the epiphyses of the humeri and femori. The ossification of the wrist showed 3 carpal centers. Marked caries and in some instances only fragments of teeth were present. The electrocardiogram revealed low voltage in all leads.



A *B*

FIG. 2.—*A*, Case 1, 17 months later. *B*, Case 2, 16 months later.

A biopsy obtained from a supraclavicular fat pad revealed a fibrolipomatous structure. The blood Kahn and the Mantoux, intracutaneous 1:1000 tests were negative. Vascular microscopy and tonoscopy (performed by Dr. Olkon) revealed capillary deficit and stasis, vasomotor instability and atherosclerotic-like manifestations. These changes were interpreted as suggestive of metabolic disharmony, nutritional deficit, and early senility. The patient did not coöperate sufficiently to determine the basal metabolic rate.

The boy was seen 17 months later (Fig. 2*A*). His activity had improved, he talked more, walked, and carried out simple commands. He received 2 grains of thyroid a day without ill effects.

CASE 2. F. D., a 22-year-old white male, brother of the former, a typical sporadic cretin, entered the Research Hospital in March 1940. He was a full-term infant, second born of a normal 9-month pregnancy with a 1-hour labor. When the boy reached the age of 3 years he was hospitalized because he did not grow and develop like the first child. His skin was dry, tongue large, as were also the head and abdomen. He remained in the hospital for 1 year, at the end of which time he sat, walked and ate by himself, all of which he could not do before. From the age of 4 until the present time the boy's condition was neglected.

Upon entrance, F. D. weighed 46 pounds and was 38½ inches tall, and was readily recognized as a typical cretin (Fig. 1*B*). He spoke only in monosyllables, carried out a few simple commands, and had an intelligence quotient of a 3-year-old.

In a recent report by one of us,[6] this patient was adequately described and therefore we will dispense with the details of the history, physical examination and laboratory findings.

The patient was last seen (Fig. 2*B*) at the same time as his brother. He weighed 47 pounds and was 43 inches tall. He was no longer constipated, obeyed commands, was more congenial, and his color had likewise improved. This patient received 2 grains of thyroid extract daily without ill effects.

Comment and Summary. Two brothers who were readily identified as typical cretins are reported from a family that had a history of frequent thyroid trouble. This is the first time we have encountered this separation in an experience with some 60 thyroid deficient children. Review of the American literature indicates the rarity of this condition.

These brothers, in addition, exhibited epiphyseal dysgenesis which has been adequately reported in the recent literature[13,18] and therefore needs no comment on our part.

We wish to emphasize the degree of improvement made in both boys, but especially in the 23-year-old one, who tolerates his thyroid medication well.

In addition we were able to obtain a biopsy of the supraclavicular fat pad, and perform vascular and tonoscopic studies.

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POST-OPERATIVE ACHYLIA PANCREATICA: FAT AND PROTEIN ABSORPTION WITH AND WITHOUT REPLACEMENT THERAPY

REPORT OF A CASE

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SINCE Allen Whipple[8] demonstrated that the head of the pancreas can be successfully resected, interest has been revived concerning the importance of the pancreatic enzymes in the digestion and absorption of food. Beazell, Schmidt, and Ivy[2] recently reported 4 cases of achylia pancreatica as the result of chronic pancreatitis which had been studied with and without replacement therapy. They pointed out that the number of such properly diagnosed and well studied patients are few, and that the general impression that oral pancreatic enzyme therapy in man is not of value is inconsistent with the results of animal experimentation. In each of their 4 cases they demonstrated that (1) the pancreatic enzymes were absent from the duodenum, (2) an excess of both fat and nitrogen was present in the feces, (3) increased absorption of both took place when substitution therapy was instituted, so that the quantity of fat excreted in the stool was decreased by 63%, and of nitrogen by 62%. Clinically, there was a decrease in the frequency and bulk of the stools, gain in weight and increased strength. They gave a daily dose of 24 gm. of their pancreatic preparation which they estimated replaced only about 15% of the normal daily secretion.

Whipple and Bauman,[9] on the contrary, as the result of their experience with patients in whom the head of the pancreas had been resected for carcinoma, concluded that normal fat absorption is possible when no pancreatic juice enters the intestine. They reported studies in 4 such patients in 1 of whom an autopsy revealed no pancreatic communication with the small intestine. They believed it safe to assume, because of the operative procedures, that their other patients also had no pancreatic juice in the intestine, although in 1 case they state that the gastric contents showed considerable trypsin and some lipase, which they suggest may be the result of a compensatory increase in the activity of other glands. However,

Koskowski and Ivy's[4] work on depancreatized dogs does not support this theory.

We recently had the opportunity of studying the fat, protein, calcium and phosphorus absorption in a patient, following resection of the head of the pancreas for carcinoma. The total absence of pancreatic enzymes following operation was demonstrated by examination of the jejunal contents both before and after the intravenous injection of secretin.

Method. The technique of Ågren and Lagerlöf[1] was used to obtain, by means of a double lumen tube and constant suction, the contents of the upper jejunum uncontaminated by gastric juice. The effects of oral administration of 24 gm. a day of a potent pancreatic preparation* were determined. We then reduced the dosage to 12 gm. a day, to note the effects of a smaller dose. Shortly after this was done a biliary fistula developed and bile disappeared from the feces. The study was continued, however, in order to observe the effectiveness of replacement therapy in the absence of bile (period IV).

Case Report. E. G., a 25-year-old female with previous good health, was admitted on June 20, 1941, complaining of attacks of epigastric and right upper quadrant pain for 1 year, not related to meals and without nausea or vomiting. Following the last attack 3 weeks previously, she developed anorexia, clay-colored stools, dark urine, pruritis confined chiefly to the feet, and lost 7 pounds in weight.

Examination showed jaundice, right-sided abdominal spasm, an enlarged liver, and a hard fixed mass 3 cm. in diameter above the umbilicus.

The icteric index was 17 and rose to 30; urinalysis showed a slight trace of albumin and was strongly positive for bile; she was slightly anemic, the white count and differential were normal. The stools were at first brown, later grayish and soft and contained no blood. The blood prothrombin level rose from 41% to 85% after an intramuscular injection of vitamin K.

Laparotomy revealed considerable enlargement of the right lobe of the liver, and tremendously dilated gall bladder, cystic and common ducts. There was a large, hard, nodular growth involving the head of the pancreas and several large lymph nodes were present along the superior mesenteric vessels.

The following operations were performed in two stages: Ligation of the common duct, cholecysto-jejunostomy and jejuno-jejunostomy (end to side), with biopsy of mass. Posterior gastro-enterostomy with resection of the first and second portions of the duodenum with entire head of the pancreas, and a partial gastrectomy were done one month after the first operation.

Histologic examination of the mass removed at operation showed the presence of a medullary carcinoma of the pancreas with metastases to the regional lymph nodes.

The last operation was performed on August 11, 1941. The jaundice cleared, but she was uable to regain weight in spite of a good appetite, and passed 2 or 3 soft, bulky, foul, grayish stools daily. On October 16, 1941 there was a rise in temperature, abdominal pain, and jaundice, and a biliary fistula opened in the operative scar. This promptly subsided and the jaundice cleared until November 8, 1941, when these symptoms recurred and lasted for about 10 days, during which time bile disappeared from the stools. These episodes were thought to be due to stagnation of bile in the stump of the common duct which acted as a valve to close off the cystic duct and thus prevented passage of bile between the gall bladder and the jejunum through the operative anastomosis.

* Holadin, in 5 grain enteric capsules, was supplied by Fairchild Bros. & Foster.

Liver function tests remained normal. Glucose tolerance tests, both oral and intravenous, gave normal curves.

At the present time, one year following the second operation, the patient has begun to complain of symptoms, similar to those at the onset of the illness, which indicate the probable recurrence of the carcinoma.

Methods of Study. Studies of the fecal loss of fat, nitrogen, calcium and phosphorus were conducted in 4 periods of 3 or 5 days each. The first 2 periods were control determinations without pancreatic enzyme administration. In period III, 24 gm. of pancreatic extract (Holadin) in enteric coated capsules were given daily, 4 gm. before and 4 gm. after each meal. In period IV, 12 gm. of Holadin were given daily. On the day preceding this period the patient became jaundiced and remained so during the 5 days of collection. No bile was present in the feces. Carmine red was given at the beginning and end of each period to mark the stools which were collected quantitatively, dried and analyzed by standard methods for fat, nitrogen, calcium and phosphorus.

Results. The results of these studies are summarized in Table 1. The average daily fecal nitrogen of normal individuals on liberal diets does not exceed 2.3 gm. and the average fecal lipid is between 7 and 10 gm.[2] The analyses in periods I and II without enzyme therapy showed a marked loss of nitrogen and fat in the feces.

TABLE 1.—EFFECT OF PANCREATIC ENZYMES ON EXCRETION OF FAT, NITROGEN, CALCIUM AND PHOSPHORUS IN THE STOOLS

(Average Daily Excretion in Grams and as Per Cent of Intake)

Period	Treatment	Dry weight feces	Fat		N		Ca		P	
			Gm.	%	Gm.	%	Gm.	%	Gm.	%
I*	None	102	49.0	65	4.6	38				
II†	None	132	70.7	71	6.5	54	1.06	106	0.95	63
III†	24 gm. Holadin	62	28.2	28	2.3	16‡	1.0	100	0.67	45
IV†	12 gm. Holadin	96	44.8	45	3.1	23‡	1.14	114	0.74	50

* Diet—protein 75 gm., fat 75 gm., carbohydrate 250 gm.
† Diet—protein 75 gm., fat 100 gm., carbohydrate 300 gm., calcium 1 gm., phosphorus 1.5 gm.
‡ N of Holadin added in intake in computing percentages.

This loss in period II represents 801 calories a day. When Holadin was given this loss was greatly reduced, in the case of nitrogen by 65% and of fat by 60%, a result almost identical with that obtained by Beazell, Schmidt and Ivy (nitrogen 62%, fat 63.3%). The dried weight of the feces was decreased by 59%, and an average of 490 calories a day otherwise lost in the stool was made available. In period IV, when bile was absent from the intestine and 12 gm. of pancreatic extract were given, analysis of the feces showed a loss of 45% of the fat intake and 25% of the nitrogen, as against a fecal loss of 71% of fat and 54% of nitrogen in period II when bile was present but pancreatic enzymes were not. This indicates that in the absence of bile pancreatic lipase is still effective in promoting absorption of fat.

During period III, when pancreatic enzymes were given and bile was present, the stools were normal in appearance and the patient felt stronger and gained weight.

In a second patient with carcinoma of the head of the pancreas successfully treated by resection of the pancreas by Dr. W. D.

Andrus, steatorrhea also developed. When 12 gm. of Holadin were given to this subject daily the fecal fat loss decreased from 31 to 21 gm. and the nitrogen excretion from 3.7 to 2.7 gm. per day. The total weight and water content of the stools were also decreased.

Calcium and Phosphorus Excretion. In all of the periods the fecal excretion of calcium was approximately equal to the dietary intake so that the patient must have shown a continued negative balance of calcium during this study. The association of increased fecal loss of calcium with steatorrhea is well recognized.[6] The lack of effect of pancreatic enzyme administration upon intestinal absorption of calcium despite the marked improvement in the absorption of fat is of interest. Even during period III, in which 24 gm. of Holadin were given daily, the fecal excretion of fat, although diminished, is still abnormally high and may account for the continued loss of calcium. A second explanation may be that a deficiency of vitamin D existed as the result of long standing steatorrhea and was not corrected during the short period in which pancreatic enzymes were given.

The fecal excretion of phosphorus was somewhat increased during the period in which no treatment was given, and was reduced to a more nearly normal value when Holadin was given.

Vitamin A Absorption. Vitamin A absorption tests were made before pancreatic enzyme treatment was started and also with treatment. The concentration of vitamin A in the plasma was determined by the method of Kimble[3] in the fasting state and 3 and 5 hours after the oral administration of 300,000 units of vitamin A. The results are shown in Table 2. In normal controls a marked rise in the plasma vitamin A is found following the administration of the vitamin A concentrate. In the initial test in this patient the fasting level is within normal limits. However, there is no rise following the ingestion of the vitamin A. When pancreatic enzymes were given, the fasting level was found to be higher than in the pretreatment period and a gradual increase in the concentration of vitamin A in the plasma was found subsequent to the administration of vitamin A. The impaired absorption of vitamin A shown by this patient is in agreement with the findings of May and McCreary[5] in children with pancreatic fibrosis, and with those of Ralli, Pariente, Flaum and Waterhouse[7] in depancreatized dogs.

TABLE 2.—VITAMIN A ABSORPTION IN THE UNTREATED STATE AND FOLLOWING ADMINISTRATION OF PANCREATIC ENZYMES

(Plasma Vitamin A—Micrograms per 100 cc.)

	Fasting	3 hours	5 hours
Patient—Untreated	48	44	39
Patient—Holadin, 24 gm. a day for 16 days	77	84	94
Normal females	38–62	..	189–720

300,000 units of vitamin A in a concentrated solution in oil given orally following drawing of initial blood specimen.

(These determinations were made by Dr. Walter R. Golden of the Department of Public Health and Preventive Medicine.)

Conclusions. 1. A case of successful resection of the head of the pancreas for carcinoma in a woman of 25 years is reported.

2. The total absence of pancreatic enzymes from the jejunum was demonstrated.

3. A marked loss of fat and nitrogen and an abnormally high excretion of calcium in the feces were found.

4. The fecal loss of protein and fat was markedly diminished by oral replacement therapy, but the calcium loss was not materially affected during the short period of observation. Clinical improvement and gain in weight occurred. The defective absorption of vitamin A in this patient was also improved during the period of pancreatic enzyme therapy.

5. The findings during a period of obstructive jaundice suggest that pancreatic enzymes are active in the absence of bile and are relatively more important than bile in the utilization of fat.

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A NOTE ON THE EVALUATION OF PRIVINE HCL AS A NASAL VASOCONSTRICTOR

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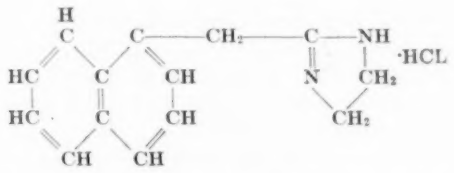
In the light of recent advances in nasal physiology and the attendant efforts to improve nasal medication, the introduction of Privine HCL as a nasal vasoconstrictor may prove of interest. Privine HCL* belongs to a new series of imidazoline derivatives recently synthesized and investigated for their biologic effects.[3] Chemically a 2-naphthyl-methyl imidazoline, it is a crystalline, colorless substance, melting at 252°–253° C., and is readily soluble in either water or saline solution. Privine HCL has the following structural formula:

* Privine HCL was supplied by Ciba Pharmaceutical Products in the form of an aqueous, isotonic, buffered solution containing phosphates, chlorides and dextrose to preserve the pH and the isotonicity.



More specifically, Privine HCL acts on the peripheral vascular bed by vasoconstriction. From the point of view of its use as a nasal vasoconstrictor, Privine HCL 0.1% is isotonic and possesses a pH 6.2. This is a pH value which approximates the pH of nasal secretions *in situ* in individuals with clinically normal noses. Experimental studies were undertaken to determine (1) its action on the cilia of laboratory animals, (2) its effect on the nasal pH of human subjects with acute rhinitides and acute rhino-sinusitis, and (3) its clinical effect on the nasal mucous membrane of individuals with nasal congestion, acute rhinitis, acute and chronic rhino-sinusitis, and allergic rhinitis.

Method. For the purpose of determining the relationship of this medicament to ciliary activity, 10 frogs and 4 dogs were employed. Ciliary action was studied in two sites—the bucco-pharyngeal mucous membrane of frogs and the tracheal mucous membrane of dogs. After bathing the selected sites in Ringer's solution to wash away blood and mucous secretions, the effect of Privine HCL on ciliary action was determined by evaluating the rate at which cilia lining the membrane carried a light object a given distance before and after application of a solution of the drug. Control tests were undertaken with normal saline, Ringer's solution, and Locke's solution. A solution of 0.1% Privine HCL was found to act favorably on ciliary activity and at no time appeared to be detrimental to it.

The relationship of Privine HCL to nasal pH was the subject of an investigation involving 10 human subjects. In his book, "The Technic of Medication," Fantus[2] asserts that a hydrogen-ion concentration near that normal to the mucous membrane is a matter of even greater importance for applications to the mucous membranes than the matter of isotonicity. Elsewhere, Fabricant[1] has reported the use of a silver-silver chloride glass electrode in conjunction with the Coleman electrometer for the determination of nasal pH. This apparatus revealed that the pH of nasal secretions in contact with nasal mucous membrane in a clinically normal nose ranges from approximately 5.5 to 6.5. Intranasal instillations of Privine HCL 0.1% at no time disturbed the normal, physiologic pH values of the individuals observed who had clinically normal nasal passageways. In those individuals who had a slightly alkaline nasal pH, namely those with acute rhinitides and acute rhino-sinusitis, instillations of Privine HCL 0.1% reduced the alkaline nasal pH to a slightly acid level approximating the normal pH of the nose.

Over a 9 months period 104 human subjects were studied clinically, besides many others who have received the material occa-

sionally. In order to determine its value as a vasoconstrictor in conditions for which this type of medication is customarily prescribed, the Privine HCL 0.1% solution was tested on individuals with nasal congestion, acute rhinitis, acute and chronic rhino-sinusitis, subacute and chronic ethmoiditis, and allergic rhinitis. The method of application included the following procedures: instillation by means of the displacement method; instillation in the head-low posture; instillation into the paranasal sinuses; tampons; sprays; applicators; and as nose-drops for home use.

Of the series of 104 patients, 50 individuals with acute rhinitis were observed during the early stages at a time when engorgement of the nasal mucous membranes was a dominant symptom. In 25 of these patients, the medication was instilled into the nasal cavity with the patient either in the head-low posture or in the displacement position. In the remaining 25 individuals, tampons saturated with the Privine solution were placed in the nose for a period of 20 minutes while the patient was exposed to an infra-red lamp. Displacement therapy was instituted in a group of 25 patients with residual rhino-sinusitis following acute nasal infection, chronic rhino-sinusitis, and subacute and chronic ethmoiditis. In 15 patients the medication was instilled into the maxillary sinus following irrigation, and in the remaining patients of the series, 14 in number, the Privine solution was employed both in cases of allergic rhinitis and during the course of postoperative nasal treatment.

The Privine HCL solution proved to be an effective nasal vasoconstrictor when used in individuals with acute rhinitis. The action observed after spraying the nose and during the enumerated methods of application is that of decongestion. The nasal mucous membrane shrinks satisfactorily and this action exists for fully as long a time as that produced by solutions of ephedrine in physiologic saline. On a number of occasions, the shrinking action appeared to last longer. Many patients seemed to prefer the Privine HCL to ephedrine and ephedrine-like nasal preparations which they had used for home treatment on other occasions. Employed as a displacement vehicle, the results obtained with Privine HCL were as satisfactory as those obtained with ephedrine in physiologic saline. Instillation into the paranasal sinuses following irrigation, however, produced no apparent changes in the status of the sinus infection.

When instilled into the nasal cavity, when sprayed or inserted as tampons, solutions of Privine HCL 0.1% appeared to be free from local mucous membrane side-effects such as tingling, smarting and burning. The toxic side-effects sometimes ascribed to overdoses of ephedrine in physiologic saline, namely, apprehension, insomnia, tremor, cardiac palpitation, urinary retention and skin eruptions, were not observed in any of our series of 104 patients.

Summary. A 0.1% solution of Privine HCL is isotonic and has a pH of 6.2. It is a non-toxic nasal vasoconstrictor which is not

detrimental to ciliary activity, and its pH approximates the normal nasal pH of the human being. Its use in rhinologic practice has been entirely satisfactory in our hands.

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THE USE OF HEXENE–OL IN BURNS OF LIMITED AREAS

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Hexene–ol (C_6H_9OH) is a fatty alcohol derived as an oxidization product of hydrocarbons and was discovered in the development of synthetic rubber. This product is a light brown, semitranslucent, solid, fatty, soft substance with a melting point of 75° F. It is non-irritating and non-toxic. Friction or stirring changes melting Hexene-ol from a light brown to a light cream color. On solidifying this light cream color will last until the product is melted again. Hexene-ol was used both as a stearified substance with 1% zinc stearate and in its natural state. The therapeutic results were the same with the plain and the stearified Hexene-ol. This study comprises the use of Hexene-ol in regional burns and does not include burns that produce shock. It was not feasible to make comparative studies with other current methods for treatment of burns at this time.

Applied to the normal skin, Hexene-ol produces an increased localized perspiration over the area covered. In this respect it resembles histamine. The warmer the room temperature, the more profuse the localized perspiration becomes; it drips from the medicated area, even though the surrounding skin may be comparatively dry. It does not produce hyperemia. The increased perspiration is caused by direct stimulation of the sudoriferous glands or by stimulation of the sympathetic nerve fibers. The amount of perspiration produced is variable in different individuals, being greater in some than in others.

Prior to the use of tannic acid,[3] gentian violet[1] and other dyes,[2] and more recently sulfadiazine,[4] fatty, oily, greasy and waxy substances had been in wide use. All of these substances form an occlusive dressing and in this manner reduce the pain caused by a burn. Hexene-ol has an analgesic effect that goes beyond the stage produced by mere application of an oily substance to the burned skin. The pain is relieved in from 1 to 15 minutes after the application of Hexene-ol—usually less than 5 minutes. The healing is

unusually rapid and scarring is reduced to a minimum. None of the burns became secondarily infected after the application of this drug.

Most of the burns treated with Hexene-ol in this study were those sustained in industrial plants. In one plant, 150 burns were treated. The patients were maintenance men and foundry men. The sources of their burns were hot metal, hot rivets, hot gears, hot or boiling water, hot oil, steam pipes, soldering irons, hot solder, etc. The majority of the burns were either first degree or first and second degree burns. Two of the men had third degree burns—one on his foot from a white hot rivet, the other over all of his right forearm from a hot gear. The first degree burns cleared up in 24 to 48 hours. The second degree burns were cured in 5 to 7 days. The third degree burns took 14 to 18 days. None of them lost any time from their work. In all of these cases, Hexene-ol was applied immediately after the burn was sustained. The relief from pain was almost immediate—to within 5 minutes from the time of application. The incident of second and third degree burns was considerably less after the application of this drug than was the case when a proprietary burn ointment was used. Hexene-ol prevented undue damage to the burned skin, and many burns remained first degree that might otherwise have become second degree burns. Oil, grease and often grime were removed by the Hexene-ol when applied to the burned areas.

In another industrial plant, 6 maintenance men had 32 burns in a period of less than 2 years. Here the causes of the burns were steam pipes, hot water, hot solder and soldering irons. These burns previously were usually second and third degree in character and the burned areas would take 2 to 4 weeks to heal. The men carried a jar of Hexene-ol in their work kits. The drug was applied immediately after the burn was sustained. This invariably prevented blistering. Healing occurred in 24 to 48 hours. Here also the second degree burns were healed in 5 days to 1 week. One of the men slipped and his right arm was immersed to the shoulder in a vat of hot water kept at a constant temperature of 190° F. By the time he had pulled his work shirt off there were several blisters on the arm and it was red from the shoulder to the fingertips. The pain was relieved in less than 5 minutes after application of Hexene-ol. He was back at work within ½ hour. The next morning the erythema was completely gone. The vesicles had healed within 1 week. Here also no time was lost from work except ½ hour by 1 man. In this plant, Hexene-ol is now preferred to the other burn ointments which had formerly been used.

The drug was placed in the kitchen of a large restaurant and was used by the chefs. During the observation period, 6 of the men suffered 8 burns. These were obtained from boiling soups, hot grease, hot pans and skillets, and in 1 case from a book of safety

matches. The majority of the burns were on the hands and forearms, most of them fairly extensive. In 1 case both forearms were involved. Healing of all the burns took place in 3 to 10 days. There was no blistering—merely peeling without scar formation. In the case of the burn with safety matches, the left thumb and its interdigital web were severely burned. The pain stopped in less than 1 minute after application of Hexene-ol, and the burn was healed in 4 days. At the end of 1 week there was slight peeling only.

Various burns were treated with Hexene-ol. One of these was sustained by a physician who picked up some glass equipment which he had constructed and which had been white hot but a few moments before. He burned his thumb and several fingers painfully. Hexene-ol was applied immediately. The pain was relieved within 5 minutes. Peeling occurred 1 week later. There was no scar.

Another case was that of a colored woman whose face was splattered with hot grease. The burns were severe enough to cause loss of pigment in the burned areas. There was complete healing in 1 week. Two patients were burned by hot skillet handles, 1 by a hot furnace door and another by boiling water. The pain in all of these was relieved within 5 minutes and healing took place in 2 days. One woman, while pouring hot molten lead into a mold, spilled some of it on her foot, sustaining a third degree burn. This was completely healed in 2 weeks. Another woman sustained first, second and third degree burns on the dorsum of her right thumb and wrist from a hot flat iron. In this case Hexene-ol was applied 4 hours after the burn was sustained. Pain was relieved in 10 minutes. The first degree burn healed in 24 hours, the second degree in 3 days and the third degree in 12 days. She developed a bright red papular dermatitis from the drug, which however cleared up in 5 days.

There was record of 15 burns treated in the hospital Emergency Room. I was able to get in contact with 10 of the 15 patients. One of these (the sulphuric acid burn) will be reported later under "chemical burns." Hexene-ol was applied to these patients 15 minutes to 24 hours after the burns were sustained. It took longer to relieve the pain in these patients, approximately 10 to 15 minutes, and slightly longer to obtain a cure than in those cases in which Hexene-ol was applied immediately. Three of them sustained their burns from gas exploding in their stoves on ignition. Two were first degree burns and the third had first and second degree burns. One was treated 1 hour after being burned and 1 hour later was back at work. The other was treated 24 hours after being burned. She was completely well in 2 days. The patient with first and second degree burns was cured in 8 days; there were no scars.

A bus driver removed the radiator cap of an overheated motor and suffered first and second degree burns on his right hand. These

were treated 1 hour later at the hospital Emergency Room. Healing was complete in 1 week.

Three infants were treated for burns. The first, 7 weeks old, had first and second degree burns on her right hand, back of scalp and interscapular region. The pain was relieved within 15 minutes. Healing was complete in 10 days. The second was a 10 months old infant who received first and second degree burns on his left cheek, right arm and chest from hot coffee. The pain was relieved in 15 minutes. There was peeling 1 week later and the burns healed leaving no visible scars. The third infant, 14 months old, was badly burned by hot fat spilled from a skillet. He received first and second degree burns on his scalp, face, right arm and hand. The vesicles were then ruptured and Hexene-ol was applied. The pain was relieved in 15 minutes. Two days later he was out of doors playing. He was cured in 9 days. Later he had no visible scarring.

A colored porter who tripped and fell while carrying a pail full of boiling water sustained first and second degree burns of his left arm and hand. Pain was relieved in 10 minutes after application of Hexene-ol. There was no visible scarring left in 2 weeks.

The last of the patients treated in the hospital Emergency Room sustained first and second degree burns on both hands and wrists and also his face from a blow torch explosion. He first applied a well-known proprietary burn remedy. When he had had no relief from the pain 1½ hours later, he came to the hospital for treatment. Ten minutes after the application of Hexene-ol the pain was gone. He returned to his work. One week later he removed the bandages. There are no visible scars left.

It was thought inadvisable to treat extensive and severe burns with Hexene-ol since the drug produces localized perspiration, and it was not known how much body fluid loss might occur. However, 2 patients with extensive burns were partially treated with the drug. The first of these patients was a young man who fell into a vat of boiling dye. He had first and second degree burns of face, shoulders, arms and legs. The first degree burns were treated with Hexene-ol. These cleared up in 2 days. The second degree burns were treated with alternate spraying of tannic acid and silver nitrate. Eventually this coagulum had to be removed because of infection under it.

The second patient was a negro who received second and third degree burns from the explosion of a blow torch. The burns involved his face, both arms and the left thigh. Hexene-ol was applied to his face and right arm, which had second and third degree burns. The left arm and thigh had third degree burns and were treated with frequent and alternate spraying with tannic acid and silver nitrate. The face and right arm were healed in 2 weeks. The left arm and leg had eventually to be skin-grafted. Since the burns of the left arm and leg were more severe than the right arm and the face, fair

comparison cannot be made. However, the case does show the efficacy of Hexene-ol in burns.

There was a third patient in the hospital who had sustained a third degree burn, 5 cm. in diameter over the right iliac spine. This was obtained from a hot water bottle 3 days prior to admission to the hospital for treatment of renal calculi. Hexene-ol was applied 1 week after admission to the hospital, when other remedies had failed to promote any healing. The burn was healed 8 days later. The subsequent scar looks more like vitiligo than like a scar due to a burn.

Chemical Burns. Two patients burned with sulphuric acid were treated with Hexene-ol. One of them had his face splattered with boiling sulphuric acid. The acid was washed off with water and he was treated with Hexene-ol 15 minutes later in the hospital Emergency Room. The pain was relieved in 10 minutes and the lesions peeled for 10 days. No visible scars were left. The other patient was a boy of 13. He was riding home on his bicycle with a bottle of sulphuric acid in his pocket; the stopper came out and the acid spilled, burning his leg from groin to knee. The acid was washed off with water and Hexene-ol was applied. Within 4 days an ulcerated area $7\frac{1}{2}$ by 10 cm. was left on the anterior surface of the thigh. The rest had healed. The ulcer was healed in 3 weeks, leaving a smooth, soft, flexible scar that 1 year later is scarcely visible.

There was 1 burn from caustic soda that was healed in 24 hours. Another burn from hot resin was healed in 2 days. There also was a burn from glacial acetic acid which was present for 3 hours before being detected. This was cured in 3 days.

Burns From Carbon Dioxide Ice. I treated 2 infants, 7 and 9 months of age, who had cavernous vascular nevi, with CO_2 ice. Thirty seconds of light pressure produced vesiculation on each of these infants. Then each of them had 3 more applications of CO_2 ice, using light to moderate pressure 30 seconds, as in the first instance, but immediately after the treatment with CO_2 ice, Hexene-ol was applied. The mothers were instructed to continue to apply Hexene-ol twice a day. This completely prevented vesiculation. The burned areas peeled for 1 week to 10 days. There was no subsequent pain or restlessness on the part of the child. The cosmetic results were very good. However, in the case of an adult who had numerous lesions of senile keratosis on both hands, Hexene-ol did not prevent vesiculation when CO_2 ice was applied with firm pressure for 60 seconds, but there was no pain and the lesions healed in 10 days.

One patient had a wart 8 mm. in diameter removed by short wave cautery. The resultant ulcer healed in 10 days with application of Hexene-ol. This patient developed a dermatitis from the drug, which was cleared up in 3 days.

Sunburn. The results obtained by using Hexene-ol in sunburn were very satisfactory. A total of 14 patients were treated for this type of burn. One of the patients was burned through over-exposure to an ultra-violet lamp. Most of them were severely burned, over two-thirds of the body surface being involved. Several of them had vesiculation. The pain and burning sensation were relieved in 10 minutes after application of Hexene-ol. Two of the patients did not use the drug until 2 days after they were sunburned. Both were bedridden, 1 with crusted lesions on his back from ruptured vesicles. Both had used proprietary and semiproprietary burn remedies without results. Both had complete relief in 10 minutes and resumed their work the next day. The skin of the patients with the vesiculated lesions took 1 week to return to normal. The others took 2 to 4 days. One patient used Hexene-ol as a preventative against sunburn. Since his skin never tanned, but always became a bright, fiery red on exposure to the sun, he had to limit the time spent bathing at southern beaches to very brief periods. By applying Hexene-ol before going to the beach, he was able to spend a greater part of the day there without any ill-effects.

Summary and Conclusions. A series of 238 burns treated with a new drug, Hexene-ol, was observed and reported. Included were 14 cases of sunburn, 6 chemical burns, 8 carbon dioxide ice burns and 1 burn from a short wave cautery.

It was found that (1) when Hexene-ol was applied soon after the burn was sustained, vesiculation was prevented; (2) the relief from pain was prompt and lasting, although the drug does not produce a local anesthesia; (3) the healing was rapid and compared favorably with any preparation used by us in the treatment of burns; (4) secondary infection was prevented; (5) the incident of irritation from the drug was moderate, being less than 1% in this series.

Hexene-ol is particularly recommended for burns of limited areas, especially those incurred in industry and household. In our experience it is the best medicament to use in these cases. It is also of value in sunburn. Further investigation must be undertaken before its value can be determined in extensive burns accompanied by shock.

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BOOK REVIEWS AND NOTICES

HEMOLYTIC SYNDROMES. By WILLIAM DAMESHEK, M.D., TIBOR J. GREENWALT, M.D., RUSSELL J. TAT, M.D., and CAMILLE DREYFUS, M.D. A reprint of an exhibit sponsored by the New England Medical Center, Boston, Mass. Presented at the 1942 Convention of the American Medical Association, Atlantic City, June, 1942. Awarded Certificate of Merit for correlation and presentation of facts. Pp. 45. Privately printed. Price, $1.50.

THIS is a graphic reprint of the authors' exhibit at the A. M. A. convention last June, which well deserved its award of a Certificate of Merit among the exhibits correlating the facts of medicine and science. With the present magazine and newspaper training of the public in the rapid appreciation of a topic through the medium of graphic presentation, a publication of this kind should be useful in leading to a better comprehension of this rapidly developing field of hematology by many of our profession who are repelled by the less efficient "selling methods" of scientific textbooks and journal articles.

Some 40-odd graphs and lists are offered, illustrating the various types of hemolytic anemias and their mechanisms. This group, that has studied and written extensively on this subject, can speak with authority. We fear, however, that some of the new categories set up will not only prove confusing but may not all stand the test of time. Also, one more page, by way of introduction, would have improved what is obviously an excellent product, that we are very glad to have for reference and instruction. E. K.

A HANDBOOK OF ALLERGY FOR STUDENTS AND PRACTITIONERS. By WYNDHAM B. BLANTON, M.A., M.D., LITT.D., Professor of Clinical Medicine and Chief of the Immunology Clinic, O.P.D., Medical College of Virginia, Richmond, Va. Pp. 182; 20 illustrations. Springfield, Ill.: Charles C Thomas, 1942. Price, $3.00.

THE object of this brief volume is stated to be the assembling of material, representing a condensation of the subject of allergy as taught and practised today, to meet the needs of busy students and busier practitioners of medicine. This alone is noteworthy.

The introductory chapter on "The Fundamentals of Allergy" presents the principal theories of the allergic concept, important definitions, a brief historical sketch, influence of heredity, incidence, and a brief description of the management of the allergic patient. Subsequent chapters proceed in logical sequence and in more detail to discussions of the causes of allergy (inciting agents), resulting manifestations, with particular emphasis on the more common symptom complexes, and suggestions as to therapeutic approach and prognosis.

In general the subject matter is well presented, concise, and to the point, with a minimum of theoretical discussion. However, the chapter on "Gastrointestinal and Other Allergies" is rather too brief and sketchy in view of recent advances. Genitourinary allergy, particularly, is summarily dismissed with a brief description of possible symptomatology and the suggestion that foods of proven etiologic significance must be avoided.

Praise must be forthcoming for the useful bits of information contained in the "Appendix," wherein one finds instruction as to the preparation and

maintenance of a dust-free room, suggestions as to the avoidance of antigenic common foods, valuable recipes, and other practical hints.

This handbook should prove one of the most useful and practical thus far presented in the field of allergy. It is recommended.

M. M.

SULFANILAMIDE AND RELATED COMPOUNDS IN GENERAL PRACTICE. By WESLEY W. SPINK, M.D., F.A.C.P., Associate Professor of Medicine, University of Minnesota, Medical School. Second Edition. Pp. 374. Chicago, Ill.: The Year Book Publishers, Inc., 1942. Price, $3.00.

THIS book is a broad review of the subject of sulfonamide therapy with particular respect to the practical considerations involved in its use in medical and surgical infections. The author is to be congratulated on the timeliness of this second edition, which includes extensive consideration of sulfadiazine, the compound most recently to have found a place in general use. In the text the author makes only passing references to experimental studies, but interprets the results of these studies in terms of practical therapy. There is a comprehensive bibliography at the end of the book which should serve as a useful guide to the literature up to June, 1942. The book covers quite adequately the subject matter implied in the title and is certain to be a useful addition to the library of general practitioners and medical students. Individuals desirous of thorough acquaintance with the use of sulfonamides in specialized fields of practice will be able to use the bibliography as a guide to the current literature. J. L.

SHOCK, ITS DYNAMICS, OCCURRENCE AND MANAGEMENT. By VIRGIL H. MOON, A.B., M.Sc., M.D., Professor of Pathology, Jefferson Medical College, Philadelphia. Pp. 324; 36 engravings. Philadelphia: Lea & Febiger, 1942. Price, $4.50.

IN this book Dr. Moon has condensed the material incorporated in his first work on shock and has added a second part on the prevention, recognition and management of this condition. As in his earlier work, he has given an admirable concise account of the capillaries as they are affected by physiologic and pathologic conditions. To his former definition of shock as "a disturbance of fluid balance resulting in a peripheral circulatory deficiency which is manifested by a decreased volume of blood, reduced volume flow, and by progressive hemoconcentration," he has added "and by renal functional deficiency." One may be impelled to ask "and why not by functional deficiency in other organs as well, such as, for example, the liver?"

Dr. Moon is a strong advocate of the "traumatic toxemia" theory of the etiology of shock and it is therefore not surprising that a major portion of the first part of the book is devoted to an exposition of this concept. To the Reviewer it seems that too little attention is given to the significance of loss of blood and plasma at the site of injury and the reduced circulation which results from nervous reflexes.

The second part of the book is devoted to considerations of a practical nature. The author's viewpoint is strikingly displayed when he states "no factor in the *prevention of shock* exceeds in magnitude of importance the *prevention of absorption*. This statement has been considered thoughtfully and it is no exaggeration." This point of view is an interesting one, although it probably is not shared by the majority of those who have devoted themselves to the study and treatment of this condition.

In regard to the criteria of shock, Dr. Moon points out well that a fall in blood pressure is not useful as an early sign of oncoming shock. He maintains that hemoconcentration is the most valuable criterion. Only passing mention is made, however, of cyanosis, cold extremities or sweating. The final chapter is devoted to the use of blood, plasma and blood substitutes.

The volume is well printed, has an excellent index and a bibliography of over 400 references. N. F.

DISEASES AND INJURIES OF THE LARYNX. By CHEVALIER JACKSON, M.D., Sc.D., LL.D., F.A.C.S., Honorary Professor of Broncho-esophagology, Temple University, Philadelphia, and CHEVALIER L. JACKSON, A.B., M.D., M.Sc. (MED.), F.A.C.S., Professor of Broncho-esophagology, Temple University. Second Edition. Pp. 633; over 200 illustrations, including 11 plates in color. New York: The Macmillan Company, 1942. Price, $8.00.

THE student or practitioner who wishes detailed information relative to all conditions affecting the larynx will find this data in this book. The text and illustrations are of the usual high standard found in all Jackson publications. K. H.

HOW TO LIVE IN THE TROPICS. By VIRGINIA LLOYD HUNT. Pp. 178, many tables. New York: Harcourt, Brace & Co., 1942. Price, $2.00.

THIS handbook for travelers and prospective residents in the tropics is largely a re-hash of other publications, half understood and uncritically accepted by the author. It deals superficially with every imaginative phase of traveling and living in health and in sickness, with just enough application to the special conditions imposed by the tropics to justify its title. The most helpful part of the book is the bibliography.

E. W.

FLUORINE AND DENTAL HEALTH. Edited by FOREST RAY MOULTON; Publication No. 19; pp. 101, many figures and charts. Washington, D. C.: American Association for the Advancement of Science, Smithsonian Institute, 1942. Price, $3.00.

BECAUSE of the widespread and increasing interest in the subject matter of this monograph, its appearance is most timely. The ground covered is indicated by the table of contents: Mottled Enamel: Early History and Its Unique Features (Frederick S. McKay); Geographical Distribution of Endemic Dental Fluorosis (Mottled Enamel) (H. Trendley Dean); The Chemistry of Fluorine as Related to Fluorosis (H. V. Smith); The Investigation of Physiological Method (H. Trendley Dean); Experimental Dental Fluorosis (Isaac Schour and Margaret Cammack Smith); Removing the Stain from Mottled Enamel (Harold B. Younger); Review of the Dental Fluorosis Studies at the University of Minnesota (Wallace D. Armstrong); Fluorine and Dental Caries with Special Reference to L. acidophilus (Philip Jay); Résumé of the Fluorine-Caries Relationship (Gerald J. Cox and Margaret Matuschak Levin); Fluorosis Studies at the University of Rochester (Joseph F. Volker); and Mottled Enamel from the Standpoint of the Public Health Dentist (including the relation of fluorine to dental caries in Illinois) (Charles F. Deatherage).

The significance of these studies is twofold. First, the etiologic relationship of fluorine to mottled enamel, when present, particularly in drinking water in excess of a certain critical level, presents a problem which can be

met only by public health methods. (The general practitioner of dentistry, however, will be interested in the chapter by Dr. Younger.) Second, the possibility that by the suitable application of soluble fluorides it will be possible to control or prevent dental caries, at once awakens and holds the interest of all those engaged in combating this most common of all diseases.

The book is well edited, illustrated and printed, and the format is gratifying. Unfortunately, no index is present.

All in all, this is a book of which dentists may well be proud and which can be heartily recommended to all dentists and to public health workers interested in dental problems. J. A.

MEDICAL PROGRESS ANNUAL. Vol. III, 1942. A Series of 52 Reports on the Recent Accepted Advances in Diagnosis and Treatment Published During 1941 in the New England Journal of Medicine. Managing Editor, ROBERT N. NYE, M.D. Pp. 678. Springfield, Ill.: Charles C Thomas, 1942. Price, $5.00.

THIS volume follows along the lines of its predecessors in its inclusion of 52 different topics of general medical interest. The variety of subjects is great, including, in addition to many related topics under general medicine and some on general surgery, various odds and ends, such as Aviation Medicine, Dermatology, Anesthesia, Radiation Therapy in Gynecology. Medical Aspects of Obstetrics, Neurosurgery, Surgery of the Sympathetic System and War Medicine. Quite a long list, designed to apply to a variety of tastes.

For the most part the articles are of sufficient length to give the important features of the subject considered, and each one has a list of references, allowing for more detailed study, if desired. Shorter reviews of this sort have a definite value, differing from the longer, more comprehensive ones that appear. H. M.

THE PLEURO–SUBPLEURAL ZONE. By J. SKLADAL, Reader in General and Experimental Pathology, Caroline University, Prague; Head of the Chest Department, Bulovka Hospital, of the City of Prague; Consulting Physician, the Masary, Institute for Treatment of Lupus, Prague-Motol. Pp. 103; 11 plates. Cambridge: The University Press; New York: The Macmillan Company, 1942. Price, $2.75.

THIS is an excellent little monograph of 100 pages by a leading Czecho-Slovakian physician now a refugee in England. It is concerned with the pathology and diagnosis of disease localized to the pleura and adjacent shell of lung 2 cm. or so in thickness. The author believes that respiratory infections often consist of inflammatory changes in this zone which will be entirely overlooked unless special methods are used to detect them. Inasmuch as incipient tuberculosis may first be manifest by a so-called corticopleuritis, accurate examination of this outer portion of the lungs is essential.

Diagnosis is considered under two headings, physical and radiologic. Dr. Skladal describes a new method of auscultation, that of examining the patient after sudden forced expiration, as a specific means of detecting disease in the pleuro-subpleural zone. The mechanics of forced expiration are similar to those existing after cough, without the side effects of violent muscular activity. When even a thin strip of pulmonary consolidation exists beneath the pleura, sudden forced expiration results in an audible reduplication of the expiratory sound. This peculiar phenomena has been traced to secondary eddies in the air column at the rima glottis, which are buffered by air containing alveoli, but transmitted to the thoracic surface as a faint sound immediately following the usual sound of expiration, when

even a small strip of peripheral pulmonary tissue is consolidated. By the same mechanism, after sudden forced expiration, very fine postexpiratory showers of râles may be heard where consolidation in this subpleural zone is breaking down.

The radiographic appearance of disease in the corticopleural zone of the lungs varies from well-defined clouding of large portions of the lung fields, usually upper half, to a very faint, diffuse veiling of the lung fields that is easily overlooked. Indeed, while a well-developed corticopleurisy may show both the typical auscultatory phenomenon of the reduplicated expiratory sound, and the clouding in the roentgenogram of the lungs which the author refers to as "sugar icing on cakes," it is perfectly possible for disease in the outer zone of the lungs to exist with only one of these criteria fulfilled. The physical examination and the radiographic study thus become complementary rather than supplementary, one to the other. While this is true in all lung pathology, it is especially so where only the outer layer of lung and pleura are affected.

This little book will receive some criticism from the English or American reader because of its style. Even though written directly in English it often reads like a rather literal translation from the German. Many words and phrases will be found to have an odd relation to their context, and this may prove somewhat disturbing to the casual observer. In addition, there are many unnecessary repetitions and the entire effect is that of rendering a simple exposition in a somewhat involved and redundant manner. Be that as it may, the author's contribution is a valuable one and should be read by all students of chest disease.

R. B.

Ceylon, Exorzismus und Heilkunde. By Paul Wirz. Pp. 292; 56 figures and 87 plates. Bern, Switzerland: Verlag Hans Huber, 1941. Price, 18 Swiss francs.

During a 5-year stay in Ceylon, the author had opportunity to learn at first hand, by word of mouth, and by observation, the medical ceremonies and exorcisms of an ancient people, the Singhalese, who have lived unchanged for 5 centuries under the dominance of three different powers. Though by no means a primitive people, they appear to be as completely under the sway of unseen powers and demonic enemies as any barbarous tribe, but differ in possessing a highly developed system of magic, exorcisms and astrologic wisdom, largely committed to writing.

The book is well illustrated and obviously prepared with care and erudition. It will be of more value to students of ethnology and folklore than to medical historians, though the latter will also turn to it with profit if working in this field. The text will not appeal to the casual reader.

E. K.

A Manual of Experimental Embryology. By Viktor Hamburger, Department of Zoölogy, Washington University, St. Louis, Mo. Pp. 213. Chicago, Ill.: Chicago University Press, 1942. Price, $2.50.

The author of this manual was associated for many years with one of the most outstanding modern experimental embryologists, Prof. Hans Spemann. The directions, therefore, especially those used in amphibian material and chick material, are based upon long-effective experience. The procedures of technique are well illustrated and explained, and have been used for a number of years in the author's classes, containing graduates and undergraduates. The students are oriented in each experiment by a discussion of the significance of the experiment, a very helpful asset.

Parts I and V cover equipment and instruments, sources and care of

animals, a long list of experiments on amphibia, chick regeneration and the gradient theory. A bibliography follows each division and subdivision of experiments. A plan is also submitted for a one-semester course, and the book is well indexed. An Appendix contains reports of Harrison's well-known Amblystoma, Pollister and Moore's *Rana silvanica* and Shumway's *Rana pipiens* stages. C. P.

THE HORMONES IN HUMAN REPRODUCTION. By GEORGE W. CORNER, M.D. Pp. 265; 32 figures, 24 plates. Princeton, N. J.: Princeton University Press, 1942. Price, $2.75.

THIS is an elaboration of lectures delivered at Princeton University to a general audience. Three chapters are devoted to explanations of anatomy and physiology for those who are unfamiliar with cellular biology. The subject matter, however, is sufficiently technical to be of interest to the trained scientist; and the physician who is not a laboratory investigator should find it useful as a lucid description of research endocrinology. He will also gain from it many interesting facts in comparative physiology, and obtain historical perspective of the development of our knowledge of sex hormones.

The manner of presentation is very pleasing, almost colloquial, yet dignified. The illustrations are simple and effective. Often the text is enlivened by accounts of the drama of research. Altogether it is an unusually successful presentation of scientific intricacies to a lay audience, without sacrificing accuracy. I. Z.

CHANGES IN THE KNEE JOINT AT VARIOUS AGES. By GRANVILLE A. BENNETT, M.D., Associate Professor of Pathology, Harvard Medical School; HANS WAINE, M.D., Research Fellow in Medicine, Harvard Medical School; Graduate Assistant in Medicine, Massachusetts General Hospital; and WALTER BAUER, M.D., Associate Professor in Medicine, Harvard Medical School; Physician to the Massachusetts General Hospital; Director, Robert W. Lovett Memorial Foundation for the Study of Crippling Diseases. Pp. 125; 31 plates. New York: The Commonwealth Fund, 1942. Price, $2.50.

THIS is an interesting and stimulating book on the development of degenerative joint disease. The authors studied the knee joints of 63 individuals, ranging in age from 1 month to 90 years, obtaining their specimens by post-mortem or following amputation, and no joint abnormalities had been observed previously on physical examination. The authors give a careful description of the anatomic changes that were found in these knees by decades, and feel that in every subject beyond the age of 15 some degeneration of the joint was observable. The bone changes affected all of the articulating surfaces, especially the patella, and were demonstrated by a dulling of the articular cartilages, fibrillation, visible fissures with roughening, fraying or splitting of the surface or more severe and extensive changes of the bony, cartilaginous and fibrocartilaginous joint components, while changes in the synovial membrane were consistently less advanced. The grossly visible alterations throughout the synovial membranes were relatively slight, and occurred during the later decades.

As the degenerative process advanced, grossly visible marginal proliferations are described as due to certain definite structural and functional characteristics of the border zones between articular cartilage and synovial lining tissue.

The authors think that an infectious cause of degenerative joint disease is entirely lacking, and that the highly important advanced age factor has

not been taken sufficiently into consideration, advancing age being the most constantly observed single factor.

They conclude that there are two fundamental considerations applicable to every example of degenerative joint disease: "One is the disadvantageous biological position of articular cartilage when subjected to injury and the other concerns the effect of mechanical stress and strain incident to joint function upon a tissue whose specific means of resistance to such use has been depleted. Further investigtion in a degenerative joint process should be a combination of microscopic observation with histo-chemical methods and studies in tissue metabolism." P. C.

MENTAL ILLNESS: A GUIDE FOR THE FAMILY. By EDITH M. STERN with the collaboration of SAMUEL W. HAMILTON, M.D. Pp. 134. New York: The Commonwealth Fund, 1942. Price, $1.00.

THE aim of this much needed book is set by the Dedication: "To the thousands of anxious men and women who have mentally ill relatives, in the hope that they will find some comfort and practical guidance in these pages." Written by one of the laity, for whom the point of view of the family and the patient is more easily preserved than for the professional, whether the specialist or the distracted general practitioner, this book will do much to guide through a harassing experience, which unfortunately is said sooner or later to strike one family in five in this country. When intelligently read and reread, it should save much unnecessary suffering for those concerned. Its 18 short chapters consider the proper attitude toward mental illness of all kinds, explain the why and wherefore of the physician's advice, why hospitalize if this should be necessary, what will happen there, and what should be done when the patient is discharged (as happens to the vast majority).

Executed with the customary excellence of Commonwealth Fund production, this concise booklet will be of great service to all who have to cope with the problems of mental illness, and an inestimable boon to the families of this much misunderstood class of patients. E. K.

AN INTRODUCTION TO MATERIA MEDICA AND PHARMACOLOGY. By HUGH ALISTER MCGUIGAN, PH.D., M.D., Professor of Materia Medica, Pharmacology and Therapeutics, University of Illinois, College of Medicine, Chicago, and ELSIE E. KRUG, B.S., R.N., Science Instructor, St. Mary's School of Nursing, Rochester, Minn. Third Edition. Pp. 779; 46 illustrations and 37 color plates. St. Louis: C. V. Mosby Company, 1942. Price, $3.50.

This text is designed for nurses, being a revision of Brodie's "Materia Medica for Nurses." The first portion, dealing with pharmacy, weights and measures, administration of medicines and dosage, is well presented and valuable for the student or graduate nurse. The remainder of the book is devoted to the pharmacology of special systems (nervous, autonomic nervous, digestive, circulatory systems, etc.). These 550 pages are too much and yet too little: too much because there is scarcely room in the nursing curriculum for the details presented, and too little because more time might be spent profitably upon the experimental methods of pharmacology, the ways in which drugs modify physiologic processes and the special significance of drug actions to nurses.

The book contains many fine illustrations; however, 23 of the 37 color plates portray plants from which drugs are derived and, though time-honored illustrations, seem to have little place in this book. J. C.

THE BRITISH ENCYCLOPÆDIA OF MEDICAL PRACTICE. A. *General Survey, Drugs, and Critical Abstracts.* 1941–42. Under the General Editorship of SIR HUMPHRY ROLLESTON, B.T,. G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. Pp. 482. B. *Cumulative Supplement.* 1941–42. Under the Editorship of SIR HUMPHRY ROLLESTON. Pp. 289. London: Butterworth & Co., Ltd., 1942. Price, $10.00 (U. S. A. funds).

THE general plan of this annual encyclopedia is similar to that of previous volumes. The first volume is "divided into 3 parts, which contain respectively a series of critical surveys of various branches of Medicine, a section dealing with new developments in drugs, and abstracts from current medical publications. . . . ." Although it is considerably reduced in size from prewar volumes, it contains the same excellent type of material. The Critical Surveys "consist of a series of authoritative, signed reviews dealing in general terms with the present position of some branches of medical science and practice, and indicating the possible future developments in these . . . ." In the Drugs section, "new drugs, or modifications of old drugs, are discussed from their therapeutical and pharmacological aspects . . . ." In the Abstracts of medical literature are brought together "the essentials of a large number of papers published throughout the year ending June 30, 1941, by British, American, and other authors. As a result of the wide extent of the War, the output of European journals and other medical publications has greatly diminished. . . . ." The topics, never occupying more than a few pages, are conveniently arranged alphabetically, with the name in bold-faced type. Unfortunately, many are not up to date.

The Cumulative Supplement, which is the second volume of the pair for 1941–42, brings up-to-date the matter contained in the parent volumes. In this, also, the various topics are considered in alphabetical order; the name in bold-faced type, making them easily and quickly found.

E. K.

NEW BOOKS

The Hormones in Human Reproduction. By GEORGE W. CORNER, M.D. Pp. 265; 32 figures, 24 plates. Princeton, N. J.: Princeton University Press, 1942. Price, $2.75.

Diseases of the Liver, Gallbladder and Bile Duct. By S. S. LICHTMAN, M.D., F.A.C.P., Adjunct Physician, Mount Sinai Hospital; Assistant in Post-Graduate Medical Instruction, University Extension, Columbia University. Pp. 906; 122 engravings and a colored plate. Philadelphia: Lea & Febiger, 1942. Price, $11.00.

Chemistry and Physiology of the Vitamins. By HANS R. ROSENBERG, Sc.D. Pp. 674; many figures and tables. New York: Interscience Publishers, Inc., 1942. Price, $12.00.

Clinical Anesthesia. A Manual of Clinical Anesthesiology. By JOHN S. LUNDY, B.A., M.D., Head of Section on Anesthesia, Mayo Clinic; Professor of Anesthesia, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota; Diplomate and Member of the American Board of Anesthesiology, Inc.; Member of the Subcommittee on Anesthesia, National Research Council. Pp. 771; 266 illustrations. Philadelphia: W. B. Saunders Company, 1942. Price, $9.00.

My Self, My Thinking, My Thoughts. By K. W. MONSARRANT. Pp. 140; a few figures. London: University Press of Liverpool, Hodder & Stoughton, 1942. Price, 7/6 net.

Hemolytic Syndromes. By WILLIAM DAMESHEK, M.D., TIBOR J. GREENWALT, M.D., RUSSELL J. TAT, M.D., and CAMILLE DREYFUS, M.D. A reprint of an exhibit sponsored by the New England Medical Center, Boston, Mass. Presented at the 1942 Convention of the American Medical Association, Atlantic City, June, 1942. Awarded Certificate of Merit for Correlation and Presentation of Facts. Pp. 45. Privately printed. Price, $1.50. (See Reivew, p. 131.)

Nasal Medication. A Practical Guide. By NOAH D. FABRICANT, M.D., M.S., Associate in Laryngology, Rhinology and Otology, University of Illinois, College of Medicine. Pp. 122; 20 figures. Baltimore: The Williams & Wilkins Company, 1942. Price, $2.50.

Handbook of the Lying-In Hospital. Woman's Clinic of the New York Hospital, 530 East 70th St., New York. Pp. 158. New York: Cornell Medical College Book Store, 1300 York Ave., 1942. Price, $2.00.

This summary of instructions to medical students and interns includes: (1) Organization and duties of the house staff. (2) Organization of the out-patient department. (3) Social service. (4) Admission routine. (5) Routine for delivery and operating rooms. (6) Blood transfusions. (7) Routine laboratory tests. (8) Diets. (9) Analgesia and anesthesia. (10) Managment of complications of pregnancy. (11) Routine and clinical application of various procedures.

The Editor, Dr. A. A. MARCHETTI, is to be complimented upon both contents and form, which includes excellent paragraph headings, and numbering of most of the lesser paragraphs, all making for ready reference. The book is recommended to obstetricians and gynecologists interested in the organization of departments of obstetrics and gynecology. D. M.

Love Against Hate. By KARL MENNINGER, M.D., with the collaboration of JEANETTE LYLE MENNINGER. Pp. 311. New York: Harcourt, Brace & Co., 1942. Price, $3.50.

First Aid. Surgical and Medical. An Advanced Guide. By WARREN H. COLE, M.D., F.A.C.S., Professor and Head of the Department of Surgery, University of Illinois College of Medicine; Director of Surgical Service, Illinois Research and Educational Hospitals, Chicago; and CHARLES B. PUESTOW, B.S., M.S., M.D., PH.D., F.A.C.S., Associate Professor of Surgery, University of Illinois College of Medicine and Graduate School; Surgeon, Illinois Research and Educational Hospitals; Senior Surgeon, Henrotin Hospital; Consulting Surgeon, Municipal Contagious Disease Hospital and Bethany Home and Hospital, Chicago, and St. James Hospital, Chicago Heights. Illustrations by CARL LINDEN in collaboration with TOM JONES of the Illustration Studios of the University of Illinois College of Medicine, Chicago. Pp. 351; 92 figures. New York: D. Appleton-Century Company, Inc., 1942. Price, $3.00.

Designed primarily for medical students but supplied with simplified descriptions of anatomy and physiology to place it within the grasp of laymen, this volume is a practical, yet fairly complete, discussion of military and civilian emergencies. Unusually strong emphasis is placed upon what not to do, in every type of emergency as well as in a special chapter devoted exclusively to "don'ts." Many lucid diagrams are supplied. M. F.

Medical Clinics of North America. Symposium on Endocrinology. November, 1942. Vol. 26, No. 6. Pp. 342. Three-year cumulative index (Volumes 24, 25 and 26—1940, 1941 and 1942). Philadelphia: W. B. Saunders Company, 1942. Price, $16.00 for the year.

Mental Illness: A Guide for the Family. By EDITH M. STERN with the collaboration of SAMUEL W. HAMILTON, M.D. Pp. 134. New York: The Commonwealth Fund, 41 East 57th St., 1942. Price, $1.00.

Constitution and Disease. By JULIUS BAUER, M.D., Professor of Clinical Medicine, College of Medical Evangelists, Los Angeles, Calif.; Formerly Professor of Medicine, University of Vienna. Pp. 220; 5 illustrations. New York: Grune & Stratton, Inc., 1942. Price, $3.50.

Fundamentals of Psychiatry. By EDWARD A. STRECKER, M.D., Sc.D., F.A.C.P., Professor of Psychiatry and Chairman of the Department, Undergraduate School of Medicine, University of Pennsylvania; Psychiatrist to the Pennsylvania Hospital; Attending Psychiatrist, Psychopathic Division, Philadelphia General Hospital. Pp. 201; 15 illustrations. Philadelphia: J. B. Lippincott Company, 1942. Price, $3.00.

Introduction to the Psychoanalytic Theory of the Libido. By RICHARD STERBA, M.D. Pp. 81. Monograph No. 68. New York: Nervous and Mental Disease Monographs, 1942. Price, $2.00.

NEW EDITIONS

Surgical Pathology. By WILLIAM BOYD, M.D., LL.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S.C., Professor of Pathology, University of Toronto. Fifth Edition. Pp. 843; 502 illustrations, 16 colored plates. Philadelphia and London: W. B. Saunders Company, 1942. Price, $10.00.

Tables of Food Values. By ALICE V. BRADLEY, M.S., Associate Professor of Nutrition and Health Education, State College, Santa Barbara, Calif. Second Edition, completely revised and enlarged. Pp. 224. Peoria, Ill.: The Manual Arts Press, 1942. Price, $3.50.

Atlas of Ophthalmic Pathology. By ELBERT DECOURSEY, Major in the Medical Corps of the United States Army; Formerly Pathologist to the Registry; and J. E. ASH, Colonel in the Medical Corps of the United States Army, Curator; ROY M. REEVE, Photographer; HELEN CAMPBELL WILDER, Microscopist; LAWRENCE P. AMBROGI, Technician. Prepared at the Army Medical Museum, Office of the Surgeons-General of the United States Army, from material in the Registry of Ophthalmic Pathology. Third Edition, revised. Pp. 136. Omaha: The American Academy of Ophthalmology and Otolaryngology (1500 Medical Arts Bldg.), 1942. Price, $5.00.

Atlas of Dental and Oral Pathology. By JOSEPH L. BERNIER, Major in the Dental Corps of the United States Army, Pathologist to the Registry; JAMES B. MANN, Colonel in the Dental Corps of the United States Army, Formerly Pathologist to the Registry; J. E. ASH, Colonel in the Medical Corps of the United States Army, Curator. Prepared at the Army Medical Museum, Office of the Surgeons-General, from material in the Registry of Dental and Oral Pathology. Second Edition, revised. Pp. 178. Chicago: The American Dental Association (212 E. Superior St.), 1942. Price, $5.00.

Atlas of Otolaryngic Pathology. By J. E. ASH, Colonel in the Medical Corps of the United States Army, Curator, with the assistance of J. L. BERNIER, Captain in the Dental Corps, Assistant Pathologist; ROY M. REEVE, Photographer. Prepared at the Army Medical Museum, Office of the Surgeons-General of the United States Army, largely from material in the Registry of Otolaryngic Pathology. Third Edition, revised. Pp. 173. Omaha: The American Academy of Ophthalmology and Otolaryngology (1500 Medical Arts Bldg.), 1942. Price, $5.00.

Osler's Principles and Practice of Medicine. By HENRY A. CHRISTIAN, A.M., M.D., LL.D., HON. Sc.D., HON. F.R.C.P. (CAN.), F.A.C.O., Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University; Physician-in-Chief, Emeritus, Peter Bent Brigham Hospital; Visiting Physician, Beth Israel Hospital, Boston. Fourteenth Semicentennial Edition (1892–1942). Pp. 1475. New York: D. Appleton-Century Company, Inc., 1942. Price, $9.50.

Diseases of Children. By BRUCE WILLIAMSON, M.D., F.R.C.P. Third Edition. Pp. 370; 70 illustrations, 6 in color. Baltimore: The Williams & Wilkins Company, 1942. Price, $4.50.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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SOME CLINICAL ASPECTS OF RECENT VITAMIN ADVANCES

MUCH of the literature on the vitamins concerns problems which are not of clinical or therapeutic interest. The present review is concerned only with the more recent reports of primary clinical importance. No special emphasis has been given to the place of vitamins in pediatrics, ophthalmology, and otolaryngology, because these have been recently reviewed in the section on the Progress of Medicine.[21,70,86]

General discussion of the approach to therapy and the use of purified and synthetic vitamins has no place in this review. A general evaluation of these phases of nutrition is well discussed in textbooks[49] on treatment. However, certain of these aspects are now in the process of clarification, as exemplified by the report of the Council on Foods and Nutrition and the Council on Industrial Health of the American Medical Association.[59] These groups, working together, pointed out the fact that the general practice of industrial concerns of providing all their employees with vitamins indiscriminately is misguided. When a satisfactory study of a given industrial situation indicates the wisdom of providing vitamins for employees, the necessity for observing proper scientific limitations of such action in the particular situation is important. After an employee has been restored to a good nutritive state, the use of a good diet of natural protective foods thereafter should suffice. The Councils further indicated that nothing in their report was intended to belittle the significance of vitamins in nutrition or the value of proper use of added vitamins in improving staple foods, such as bread and flour. The purpose of the report was to discourage indiscriminate mass use of vitamins.

Vitamin A. The value of diagnostic tests in the detection of vitamin A deficiency remains a debated question. The feeling is prevalent that the standards for the photometer test are too high. Prolongation of adaptation time occurs with little apparent clinical or diagnostic significance and photometer tests do not always correlate well with blood levels.[13] Still the photometer has been found useful in diagnosis, particularly when determinations are made before and after treat-

ment.[12,27b] Similarly, although evidences of deficiency do not correlate accurately with vitamin A blood levels, normal values are not likely to occur in clinical deficiency.

A more recent addition to tests for vitamin A deficiency is biomicroscopy under slitlamp illumination. Kruse,[36] using the method on 143 persons in the low income bracket, found gross (Bitot's spots) and microscopic lesions of xerosis conjunctivæ in 45% and 54%, respectively. These he considered evidence of vitamin A deficiency and suggested that they might precede the development of night blindness. However, Berliner[6] does not consider these changes necessarily prexerotic states related to vitamin A metabolism, and Callison[10] has described vitamin A deficiency and disturbed dark adaptation without changes in the conjunctiva. Obviously, the problem requires further evaluation.

Recent work suggests that variations in reactions to standard color-vision tests may not rest entirely on Mendelian characteristics, but may be corrected with vitamin A.[19]

Sandels and associates[64] have described follicular conjunctivitis as a common manifestation of vitamin A deficiency, particularly in the age groups from 6 to 12 years. They have correlated these findings with low dietary intake, and have found 13,000 units of vitamin A daily effective in treatment.

Youmans[95] has pointed out that most vitamin A deficiency seen in practice develops secondary to some other primary disease. This is particularly true in liver disease, for important phases of the metabolism of vitamin A, for example storage, and the conversion of carotene into vitamin A, takes place in this organ. Cirrhosis of the liver,[27a] as well as infectious processes, affect storage.[57] Blood levels of the vitamin are closely linked with the liver stores, where mobilization is influenced by sympathetico-adrenal stimulation.[98]

Various infections, such as tuberculosis and osteomyelitis, increase the need for vitamin A. In tuberculosis,[7] absorption of vitamin A is also poorer than normal. It has been found that the greater the weight loss and the more severe the gastro-intestinal symptoms, the poorer the absorption of the vitamin. Autopsy findings have not explained these results. Either decreased absorption or increased destruction is produced by various diarrheas, surgical procedures, and certain gastro-intestinal disturbances. In gastro-intestinal cancer, the levels of vitamin A in the plasma have been reported below normal in 86% of the patients examined.[62] This is thought to result from both inadequate absorption and an hepatic dysfunction of storage or formation from carotene. In some patients, dietary deficiency or malabsorption could not explain the low values. Malignancies, other than those arising in the gastro-intestinal tract, may produce similar changes in the plasma levels.

Most interesting is the report on treatment of arterial hypertension[55] with vitamin A. Doses of 180,000 to 200,000 units daily, reduced later to 90,000 to 100,000 units, are reported to give a drop in blood pressure of 30 to 40 mm. of mercury. A later report from this country[87] confirms these results in experimental renal hypertension in dogs, but controlled observations in patients by Taylor, Corcoran and Page[84] do not support these results.

Vitamin B Group. Clinically, at least 8 well-known substances in the vitamin B complex must be considered. These are thiamin, niacin, riboflavin, pyridoxine, pantothenic acid, p-amino-benzoic acid, choline, and biotin. Only the first 3 are well established clinically. Experimental choline deficiency is characterized by fatty changes in the liver, and this substance is quite likely essential for man. The others are considered below.

Probable "safe" levels for daily intake of the B vitamins by human beings are variously stated. The National Research Council Committee on Foods and Nutrition[9] suggests the following for a 70 kg. man using 2500 calories daily:

Thiamin, 1.5 mg
Niacin, 15 mg.
Ribóflavin, 2.2 mg.

R. J. Williams[92a] states that a fully adequate idea of the requirements of human beings for the various vitamins could presumably be obtained only as a result of a series of extended controlled studies using man. He compared the vitamin content of a well-rounded mixed diet, such as might be recommended for human beings, the vitamin content of certain commercial animal foods, and of the carcass of the rat. On an isocaloric basis, the vitamin content agreed closely. He estimated that "safe" levels for daily intake of B vitamins for human beings, even under conditions of pregnancy and lactation, are probably represented by: thiamin, 3.2 mg.; nicotinic acid, 40 mg.; riboflavin, 3.7 mg.; pantothenic acid, 11 mg.; biotin, 0.14 mg.; inositol, 1000 mg.; pyridoxine, 1.5 mg.; and folic acid, 1 mg. Although the last 4 are not definitely known to be required by man, they occurred in foods in about the extent indicated. These figures exceed those laid down by the National Research Council Committee in thiamin, niacin, and riboflavin. Estimates for pantothenic acid have not been made by others, and the same is true for pyridoxine, folic acid, and inositol.

R. D. Williams and his associates[91] have estimated the optimal intake of vitamin B_1 at 0.5 to 1 mg. per 1000 calories in a diet in which the carbohydrate and fat have the conventional proportions. It should be emphasized that the thiamin content of the average American diet, as consumed by the middle two-thirds or three-fourths of the population prior to enriched bread and flour was about 0.8 mg. per 2500 calories.[38]

Deficiency of the B vitamins, along with iron deficiency, is probably the most prevalent today. Their occurrence in the same foods emphasizes the common finding of multiple deficiencies in the same patient. In certain instances of cirrhosis of the liver, the importance of abnormalities of the diet, particularly in protein and B complex is becoming evident. In experimental animals,[26] a type of cirrhosis characterized by focal necrosis and fatty infiltration, occasionally developing into periportal fibrosis, has resulted from diets low in B complex and protein. These changes resemble those seen in alcoholic patients. The relationship of these factors to cirrhosis of the liver in man has just recently been admirably reviewed by Wilen.[90]

Evidence is also beginning to accumulate to suggest a relationship between certain members of the B complex and the development of certain types of cancer. It is suggested that the most frequent, and probably the most important form of chronic irritation in the oral

mucous membrane, from the standpoint of cancerigenesis, is avitaminosis B.[45] The belief was stated that prophylaxis against mouth cancer would include an increase in general intake of vitamin B in foods. Relationships have also been shown between the B group and the development of experimental cancer of the liver in animals.[61] The application of these data to the study of this disease in man is anxiously awaited.

Wernicke's encephalopathy,[11] which is characterized by ophthalmoplegias, clouding of consciousness, and ataxia, found in chronic alcoholism, gastric carcinoma, pernicious anemia, vomiting of pregnancy, and other conditions, has responded to treatment with B complex.

A relationship has been reported between the endocrine glands and the metabolism of vitamin B complex.[3] Improvement has been noted in B complex deficiencies by the administration of anterior pituitary extracts when the clinical picture has not been entirely relieved by vitamin therapy. Also estrogen therapy has been noted to induce or exaggerate polyneuritis, pellagra, and cheilosis. Ashworth and Sutton[3] suggest either an increased demand for, or a suppression of utilization of, the vitamin B complex by estrogens.

The success of B complex, either as crude extract or purified mixtures in multiple B deficiency, is well established. Spies, Grant and Grant[76] describe a mixture of 25% dried brewers' yeast, 67% peanut butter, and 8% peanut oil as a protective food in B deficiencies, particularly in pellagra, beriberi and ariboflavinosis. Patients taking 60 to 75 gm. of this mixture daily as a dietary supplement showed improvement in the appetite, gain in weight, and healing of lesions.

There are on the market many vitamin B complex preparations which represent extracts of yeast and liver. Such a source is no guarantee of potency for there may be large losses in extraction. It has been estimated[92a] that to get enough of the B vitamins from such sources to equal the intake on a good diet, one would have to consume 10% of one's calories in the form of 7 to 8 teaspoons of the dry powder of one commercial extract tested. Many such preparations are fortified with thiamin, niacin, and riboflavin, but are not "balanced" in the amounts of the various components.

Vitamin B_1. Induced thiamin deficiency[91] of severe degree is associated with states of inactivity, apathy, serious derangement of metabolic processes, loss of weight, and finally prostration. Moderate prolonged restriction was associated with emotional instability reflected by irritability and moodiness, quarrelsomeness, lack of coöperation, vague fears progressing to agitation, mental depression and other signs. Mental and physical inefficiency preceded other more objective manifestations of thiamin deficiency by weeks or months. Changes in judgment and foresight have also been noted.[91]

Clinical evaluation shows that about one-third of the wage-earning families of the population live on inadequate diets, a large part of which rests in the B group, and particularly thiamin. This, coupled with losses through cooking conditions, may lead to serious deficiency. In meats, a potent source, boiling and stewing may destroy up to 50% of the thiamin. Additional need for thiamin, or diseases interfering with intake, are likely to be associated with such deficiency. The diagnosis of beriberi is often masked in such diagnoses as diabetic, gesta-

tional, alcoholic, or metabolic polyneuritis. Pellagra, sprue, celiac disease, hyperthyroidism and febrile states may have, as part of their picture, thiamin deficiency.

Thiamin is normally excreted in appreciable amounts in the sweat.[28] It has been estimated that a man working in a room of moderate temperature may sweat 2 to 3 kg. daily without visible perspiration. This would account for loss of 5% to 15% of ingested thiamin.[28]

Laboratory methods for estimation of thiamin subnutrition are not widely used clinically. This is due, in part, to a lack of simplicity as well as to variations in experimental results.[29] Total blood thiamin levels may not fall sufficiently early in deficiency to make them of value diagnostically in so-called "subclinical" states.[97] Excretion tests,[46] saturation tests, and pyruvate determinations on the blood before and after treatment have been reported as useful.

Increase in the thiamin content of the diet may be accomplished by the addition of thiamin-rich foods, lean meat, internal organs, milk and whole-grain cereals. Thiamin-poor foods may be eliminated. Enriching of basic foods in which processing has removed the thiamin content, is useful. Wheat flour and its products are estimated to contribute more calories to the American diet than any other class of food[17] and, with refined sugar and fats, account for over one-half of the caloric intake. White bread is about one-tenth as potent in thiamin as whole wheat and there are marked reductions in calcium, iron, and other factors as well. The enriching of flour to the equivalent of whole wheat is an important step in correcting deficiency produced by such refining processes, but one cannot assume such flour is superior to, or even nutritionally equivalent to, whole-grain flour. One should not be lulled into a feeling of false security in his thiamin quota by eating bread made of enriched flour. Six slices of such bread supply a little over one-sixth of the daily requirement,[17] so that other foods must be depended upon to complete the daily quota.

Thiamin has been used in the treatment of many seemingly unrelated conditions, some of which have already been mentioned. Reports of successful treatment of herpes zoster are not conclusive. Even injections locally into the areas about the eruption have been tried. Equivocal results are also reported in tic douloureaux, pernicious anemia, morphine addiction and irradiation sickness. Combined with other factors in the B complex, and at times with vitamin E, it has been used in many neurologic states which are, in general, refractory to treatment. Diabetic neuritis of the symmetric type, particularly that starting in the lower extremities, has been successfully treated by oral doses of 10 mg. daily.[22] Other types of pain, vague aches, and pain involving single nerves did not respond consistently.

Sensitization, including positive intracutaneous and passive transfer tests, to thiamin has been described.[39]

Riboflavin. Since the association of riboflavin deficiency with a distinctive clinical picture in man, there has been wide interest in this problem. Attempts have been made to establish diagnostic chemical tests for early deficiency. Blood values are of little diagnostic importance,[4] and excretion tests, as yet, are of little practical value. In early diagnosis, the recognition of the superficial vascularizing keratitis and its associated symptoms of burning, itching, blurring of vision remains

most important,[82] for this finding is described as the earliest and most common visible manifestation. While changes in the tongue and lips generally follow the keratitis, absence of the latter does not exclude riboflavin deficiency. It is interesting to note also that interstitial keratitis associated with hereditary syphilis has responded more rapidly to treatment when riboflavin is given.[14]

It has been suggested,[93] because of the recognition of widespread ariboflavinosis, that destruction of riboflavin by light at the high temperatures used in cooking might be of practical importance. Up to 48% of riboflavin may be destroyed when food is exposed to light during cooking in open vessels. Williams and Cheldelin[93] showed that, under usual kitchen conditions in a well-lighted room, destruction of riboflavin in liquid foods was rapid and that opacity tended to slow up the loss. Certainly, large losses in such foods as milk and eggs which alone contribute approximately 40% to 50% of the riboflavin in the average American diet may aggravate any shortage.[93]

Spies, Bean, Vilter and Huff[75] found ariboflavinosis to be common in children. It has been reported in the premature infant.[79] Nursing infants were satisfactorily treated by administering to the lactating mother 1 mg. doses 3 times daily or brewers' yeast or liver extract daily. Five mg. of riboflavin daily is usually adequate except in liver disease, gastric achlorhydria or diarrhea when the amount should be doubled to tripled. Sodium riboflavin may be given parenterally in 10 to 15 mg. doses.

Niacin. Recently the term "niacin" has been applied to nicotinic acid.[15] More acute forms of nicotinic acid deficiency may give rise to clinical pictures unlike that of pellagra. Such is the so-called nicotinic acid encephalopathy characterized by clouding of consciousness, progressive stupor, cogwheel rigidity and gasping and sucking reflexes. Sydenstricker and Cleckley[81] include in this group of symptoms such manifestations as lethargy, stupor, mania, hallucinations and disorientation which respond promptly to niacin therapy.

Many tests for niacin deficiency have been advocated. Blood and urine levels are of little help. There is a constant loss of at least 10 mg. of known nicotinic acid derivatives in the urine daily, regardless of diet.[66] The extra excretion of nicotinic acid and trigonelline after test doses of nicotinamide may serve as an indication of the nutritional status of an individual in respect to nicotinic acid,[56] but is not yet satisfactory as a clinical test.

The estimation of the amount of certain fluorescent substances in the urine shows promise as a test of nicotinic acid deficiency.[50] Evaluation of this test is not yet complete. One of the fluorescent substances, called F_1, was found in relatively small amounts in normal urine but in larger quantities in the urine of pellagrins. Another substance, F_2, developed fluorescence only on the addition of alkali. It was not found in the urine of pellagrins but reappeared after nicotinic acid therapy, and increased in the urine of normal subjects after administration of nicotinic acid. Animal experimentation, to obtain a purer form of nicotinic acid deficiency than occurs in patients, confirmed these results although the reciprocal relationship of F_1 and F_2 was not perfect.

Pyridoxine. Despite the fact that there is as yet no clear-cut evidence of the importance of pyridoxine in clinical nutritional defi-

ciency, the study of its metabolism in man suggests an important rôle.[68,73] The similarity of its distribution in food to other members of the B group also suggests its importance, as does the work of Williams, quoted above.

Since the report[74] that administration of pyridoxine to 4 pellagrins on a controlled diet caused the disappearance of such symptoms as extreme nervousness, insomnia, irritability, abdominal pain, weakness and difficulty in walking, its use has centered on muscular and nervous disorders, including pseudohypertrophic muscular dystrophy, myasthenia gravis, amyotrophic lateral sclerosis, Parkinsonism and others. Jolliffe[33] found it beneficial in Parkinsonism of less than 3 years' duration and without a history of encephalitis. Still others report no improvement with pyridoxine in dosage varying from 50 to 100 mg. intravenously daily or every other day, alone, or in combination with vitamin E and other factors of the B complex. In pseudohypertrophic muscular dystrophy, reports are similar. Antopol and Schotland[2] found considerable improvement in 6 cases while Keith,[34] using 100 to 200 mg. intramuscularly found no improvement. There are many difficulties in the evaluation of such therapy.[42]

Because of the reported relief of weakness in pellagrins by pyridoxine several studies have been carried out to test the effect of pyridoxine on muscular weakness. Muscular weakness brought to the point of exhaustion by performance of work has been relieved by pyridoxine in patients with neurasthenia, hyperthyroidism, and ulcerative colitis.[63] In these states, deficiency might be expected. However, in patients with severe malnutrition, tested in the same way, there was no positive response. In another report,[24] a study of fatigability carried out by the double work period method on subjects receiving "adequate" nutrition showed no immediate effect from thiamin, cocarboxylase, riboflavin and parenteral vitamin B complex.

Pantothenic Acid. The status of our knowledge of the importance of pantothenic acid in human nutrition is similar to that of pyridoxine. Its presence in all types of living cells[92b] speaks for its importance, probably as a catalyst in some step of carbohydrate metabolism. In man,[47,54,94] sufficient quantities occur in the blood for determination of blood levels, and the daily urinary excretion has been measured. Again, these facts indicate the entrance of this vitamin into the human economy. Further suggestions that pantothenic acid may be of clinical importance is the demonstration in animals that larger amounts of it and pyridoxine are necessary in hyperthyroidism.[18]

The use of pantothenic acid to restore color of graying hair is well known. Results are equivocal. Para-aminobenzoic acid, considered a part of the B complex, has also been used.[71a,b] It is known to modify melanin formation. A darkening of the hair is reported in 3 to 8 weeks with oral doses of 100 mg. twice daily. The use of these preparations is still in the experimental stage.

Biotin. So-called vitamin H, or biotin, is the curative factor for egg white injury in rats and has been considered a part of the B complex. Sydenstricker and his associates[83] placed a group of volunteers on a diet low in biotin and high in avidin, a substance which makes biotin unavailable for the organism. Definite findings were observed. In 3 to 4 weeks, a scaly desquamation appeared and lasted 7 to 10 days. In

the seventh to eighth week, a grayish pallor of the skin and mucous membranes developed. The color was out of proportion to the blood picture. Lassitude, depression, muscular pains and paresthesias, somnolence, precordial distress, and, in 2 instances, a mild panic state were observed. Biotin in 3 daily doses totaling 150 to 300 mg. controlled the symptoms in 3 to 5 days.

Vitamin C. This vitamin is one in which determinations of blood levels has become a part of clinical laboratory diagnosis. Study of induced deficiency has shown that a reëvaluation of the interpretation of vitamin C blood levels is necessary.[96] Levels previously considered indicative of scurvy, below 0.4 mg. per 100 cc. of plasma, may be found in normal individuals. Determinations on the white cell-platelet fraction and on whole blood are more reliable than determinations on plasma. High values indicate the presence of body reserves. Low values, even approaching zero, have developed in persons with 75% reserves as well as in those with scurvy. It is here that saturation tests may be of help in diagnosis.

The increased requirements for vitamin C in diseases which increase metabolic processes is evident. This occurs in such conditions as hyperthyroidism, tuberculosis, rheumatic fever, pregnancy, pneumonia, osteomyelitis, and other febrile states. In inadequate intake, or increased loss, as in diarrheas, the requirements are also evident. In addition, the use of vitamin C has been advocated in many diseases where clear-cut indications are not evident, and in most such conditions the results with its use are doubtful. Such conditions include senescence, certain types of cutaneous pigmentation, essential hematuria and chronic lead poisoning. Arsenical reactions complicating the treatment of syphilis, radiation sickness, gingivitis, corneal inflammation, fall into the same group. In all these, vitamin C has been reported as beneficial in treatment, but its importance is still not established. In anemia, thought to result from vitamin C deficiency, iron has been shown to be effective when vitamin C is not.[41] Deficiency associated with gastric lesions has been described.[44]

Vitamin D. Evidence has long indicated that rickets may be due to more than vitamin D deficiency, and may include endocrine and general nutritional factors. In certain cases of low phosphorus rickets, which are refractory to treatment with vitamin D and have associated renal lesions, it is possible[29] that the development of the rickets is due to a failure of the renal tubular mechanisms concerned with the reabsorption of phosphate. Animal studies[51] suggest that renal damage may be important in the production of evidence of toxicity from excessive dosage of vitamin D.

So-called massive dose therapy, both orally and parenterally,[85a,b] has been utilized in the treatment and prophylaxis of rickets. Curative doses of vitamin D_2 or D_3, representing 600,000 I.U. or more, have not been accompanied by evidences of toxicity. Single prophylactic doses of 400,000 to 500,000 I.U. parenterally have been given for protection for the entire winter period. Such treatment is not generally used. Several autopsies are on record[85c] of patients who had received over a million units 3 to 26 days before death. No changes indicative of hypervitaminosis D were found. While hypervitaminosis D has been produced, the use of vitamins D_2 and D_3 has not resulted in toxic

symptoms in over 600 cases. Irradiation of vitamin D preparations is thought to result also in the production of other irradiation products than vitamin D_2, which probably produce toxic symptoms. Vollmer states that the fish liver oils do not contain these toxic products. No permanent damage has been noted in the treatment of arthritis with doses of 200,000 to 1,000,000 units over periods of weeks. However, such symptoms as nausea, frequency of urination, lassitude, diarrhea, pains, anorexia and vomiting do occur.

Reports of the treatment of psoriasis and rheumatoid arthritis with vitamin D are still conflicting.[72,77] Freyberg[25] has pointed out that there is no good evidence for the existence of any antirheumatic vitamin.

Vitamin E. The importance of vitamin E in human nutrition is not yet established. Until recently its use was confined to the treatment of habitual abortions and functional sterility, and success is claimed in 75% to 80% of the cases.[8] Other forms of treatment have given equally good figures so that the value of vitamin E remains to be established. The Council on Pharmacy and Chemistry of the American Medical Association[60] has not accepted the claims in the treatment of habitual abortion.

The production of paralysis and muscular lesions in experimental animals with vitamin E deficiency has led to the widespread use of this substance in the treatment of a variety of nervous and muscular disorders, both with wheat germ oil and synthetic preparations. Muscular dystrophies and atrophies, amyotrophic lateral sclerosis, Parkinsonism and other neurologic disorders have been included. Claims of success and failure have appeared with vitamin E used alone and in conjunction with other vitamin products, especially the B group.[80] Lubin[43] applied quantitative methods to this problem. Thirty-five patients were treated with large doses of alpha-tocopherol and most were followed at intervals by dynamometric and electrical methods for muscular strength, and measurements of the creatinine and creatine output. In 31 patients, the condition remained stationary or became worse during the period of medication. In the 4 remaining patients, improvement was considered unrelated to the intake of tocopherol.

Vitamin E is said to benefit primary but not secondary fibrositis.[32,78]

Vitamin K. A great number of compounds have been found which have the activity of vitamin K. Of these, 2-methyl-1, 4-naphthoquinone is the most widely used synthetic and has been given the name "menadione." The success of this, and other preparations having the activity of vitamin K, in the correction of the low blood prothrombin levels resulting from vitamin K deficiency is without question. When low prothrombin levels in the body are sufficient to interfere with the clotting mechanism, hemorrhage results. Probably the best known example of the disturbance in this mechanism is obstructive jaundice in which the lack of bile in the gastro-intestinal tract interferes with proper absorption of vitamin K. Deficiency may occur because of inadequate diet, and in diarrhea, as in sprue, celiac disease and ulcerative colitis. Primary hepatic injury may interfere with the metabolism of vitamin K and prothrombin even when the vitamin is well absorbed. This fact has formed the basis for a liver function test utilizing vitamin K and its effect on blood prothrombin levels, for vitamin K therapy has no effect in elevating low blood prothrombin levels resulting from severe

hepatic injury. Hypoprothrombinemia occurs frequently in pulmonary tuberculosis. Low values have been reported with pulmonary hemorrhage[40] and vitamin K preparations have been suggested as useful in the control of such hemorrhage. Hypoprothrombinemia also occurs in pernicious anemia in relapse, usually in levels between 40% and 65% of normal. Vitamin K therapy is reported as unsuccessful in correcting this change[88] while there is a rise with specific liver therapy.

In the newborn, the prothrombin time is often prolonged, particularly from the second to the fifth day. This change is upon the basis of vitamin K deficiency and, if sufficiently marked, hemorrhagic disease of the newborn appears. This change is not related to the mother's diet, but prothrombin levels below those usually seen at this time may develop if sodium pentobarbital has been used as an analgesic in the mother.[23]

Despite the fact that an adequate diet in the mother does not protect the child, administration of vitamin K before delivery does. Beck, Taylor and Colburn[5] found only 5 (0.5%) of 1022 infants of mothers so treated with evidences of hemorrhage, while 21 (2%) of 1037 controls showed such evidences. This represents a reduction of 75% with treatment. In this study menadione was used in 2 mg. doses at the time of admission to the hospital for delivery and the dose was repeated at 6-hour intervals throughout labor.

How late in labor menadione administered to the mother may be effective in the newborn is an important question. Hellman, Shettles and Eastman[30] found definite elevations in prothrombin levels in the infant when vitamin K was given as late as 4 hours before delivery. In general, better results are obtained by administration of the vitamin to the mother than to the child after birth, even though the daily requirement of the newborn has been estimated as low as 1 μg. of the synthetic vitamin. In a study[65] in which these factors were analyzed, 711 of 1693 newborn infants were given vitamin K in the first 10 days of life. As soon as they reached the nursery, a 1 mg. tablet was dissolved in a teaspoon of water and given with a medicine dropper. If regurgitated, the dose was repeated. In 606 instances, the prothrombin determinations on cord blood were similar to those on the mother's plasma. The values diminished in the first 3 days and rose in the next 3, almost to reach the cord level by the seventh day. Levels did not rise above those of the cord, whereas values above these were obtained by administration of the vitamin to the mother before delivery. These authors found the frequency of conjunctival, vaginal, petechial, cerebral, and umbilical hemorrhage unchanged by vitamin K therapy.

Intravenous use of menadione and other compounds, such as tetra sodium salt of 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester,[16] and 4-amino-2-methyl-1-naphthol hydrochloride eliminates bile salt administration and responses in the prothrombin time have occurred in 1 to 3 hours.[1]

The extensive use of purified synthetic preparations, especially those given parenterally, suggests the possibility of toxicity and hypervitaminosis from overdosage. In animals[69] large doses have produced respiratory depression and congestion of organs. The usual dosage in man has produced no untoward symptoms. Methylnaphthoquinone,

1% in an ointment base, has produced dermatitis in 5 of 9 patients so treated.[53]

It is of interest to note that the prolongation of the prothrombin time resulting from the administration of dicoumarin is not corrected by menadione in 10 mg. doses.[48]

Vitamin P. A second hemorrhagic factor is known to be associated with vitamin C in citrus fruits. This compound is a flavone. Its use in both animals and man in controlling purpuras associated with low capillary resistance is reported as successful.[37,58,67] While the deficiency may occur along with vitamin C deficiency, it is unrelated in its development to vitamin C metabolism. Increases in capillary fragility in purpura associated with allergic states, infection, arsenic poisoning and psoriasis have responded to oral doses in the range of 100 to 150 mg. daily.

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NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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THE progress article in this Department will appear in the February number.

PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF NOVEMBER 17, 1942

Measurements of Uterine Contractions of 105 Patients Throughout Labor. DOUGLAS P. MURPHY (Department of Obstetrics and Gynecology, University of Pennsylvania). Uterine motility was recorded with a Lorand tocograph at intervals of 1 to 2 hours from the time that the patient entered the hospital in labor until delivery took place. The Lorand tocograph is a simply constructed mechanical device which registers the uterine movements through the medium of the anterior abdominal wall. It supplies a graphic record of this activity.

Tabulated measurements of the graphs indicated the changes in magnitude which the uterine tonus, strength, duration and frequency of the intermittent contractions undergo as labor advances, and also in what degree parity and feto-pelvic disproportion modify this activity.

The Determination of Sodium in the Glomerular Fluid of Necturi. PHYLLIS A. BOTT (Laboratory of Pharmacology, University of Pennsylvania, and Department of Physiological Chemistry, Woman's Medical College of Pennsylvania). The sodium content of glomerular fluid was compared with that of serum in a series of glomerular puncture experiments on Necturi. For use in these and other studies on glomerular and tubular fluid an ultramicro method determining as little as 0.3 microgram of sodium has been developed. The steps involved in the method are as follows: 1, precipitation of sodium as sodium zinc uranium acetate in capillary tubes; 2, washing the precipitate on special micro filters with a solution of magnesium uranium acetate saturated with sodium magnesium uranium acetate, followed by alcohol and ether; and, 3, photoelectric determination of zinc (in the Evelyn macrocolorimeter) in an aqueous solution of the dissolved precipitate by

means of the red color produced with alkaline diphenylthiocarbazone. For determination of sodium in serum the proteins are first precipitated in capillary tubes with 20% trichloracetic acid.

The sodium content of glomerular fluid was found to be within 5% of that in serum in 9 out of 15 experiments. The greatest differences were −14% and +9%. This is regarded as additional evidence that the glomerular fluid is an ultrafiltrate of plasma.

Some Effects of Tannic Acid on the Cell Surface. M. H. Jacobs, Dorothy R. Stewart and Mary K. Butler (Department of Physiology, University of Pennsylvania). Tannic acid is known to produce certain characteristic effects on molecular films of proteins, one of the most striking being the enormous decrease in permeability to ions indicated by the rise in electrical resistance and electrical capacity produced by "tanning." (Dean, Cole and Curtis: *Science*, **91**, 50, 1940). The normal permeability of the erythrocyte to certain anions can be shown to be greatly decreased by tannic acid under conditions that leave its permeability to water, fatty acids, NH_3, thiourea, glycerol, ethylene glycol, diethylene glycol, triethylene glycol and other undissociated molecules little affected. Thus the osmotic shrinkage that occurs when Cl' ions from the cell are exchanged for HCO_3' or SO_4'' ions from outside is strongly retarded by concentrations of tannic acid sufficiently low to cause no agglutination of the cells and to have little effect on their permeability to many undissociated molecules. This effect can be more or less completely reversed by adding a small quantity of gelatin to a suspension of the "tanned" cells or by washing them with gelatin-containing saline. Tannic acid has little effect on the rate of hemolysis in solutions of ammonium acetate, which can enter erythrocytes by a purely molecular mechanism; but in solutions of NH_4Cl, in which an ionic exchange is involved, the retardation may be very great. In the case of NH_4Cl "catalyzed" by NH_4HCO_3 the initial swelling, believed to be associated with the entrance of NH_3 and CO_2 (Jacobs: Cold Spring Harbor *Symposia*, **8**, 30, 1940) is unchecked by tannic acid, but the later ionic exchange of HCO_3' for Cl seems to be greatly slowed. Likewise, the peculiar volume changes produced by NH_4OH are affected by tannic acid as they should be if there were an initial rapid entrance of NH_3, followed by a later ionic exchange.

Studies on the Distribution of Potential of Ventricular Origin. Charles C. Wolferth, Mary M. Livezey and Francis C. Wood (Robinette Foundation, University of Pennsylvania). It has been shown in a previous study that the two patterns of potential variation found on the chest just external to the right and left borders of the heart remain relatively intact along lines to the corresponding shoulder tips, except for decrement as distance from the heart increases. These relationships made possible development of the procedure which we have previously called "the method of balanced potentials." By the use of this method each of these patterns can be practically eliminated from an electrocardiogram, except insofar as it may be transmitted to

the exploring electrode. Further studies by the method of balanced potentials show that there are but three patterns of potential variation with widespread distribution on the body surface. These are the two mentioned above and a pattern found below the diaphragm. On the precordium, however, there is almost infinite variation in pattern which can be demonstrated by slight shifts in position of the exploring electrode. These precordial patterns are distributed to the surface of the upper abdomen with marked decrement as distance from the heart increases.

In animal experiments using needle electrodes insulated except at the tip, it was found that in regions not more than 2 inches from some part of the external surface of the ventricles (precordium, lungs, diaphragm) slight change in position of the exploring electrode resulted in change in the pattern of potential variation. Reduction in magnitude of potential variation was rapid as distance from the heart increased. However, on peripheral areas of the diaphragm, abdominal organs, abdominal wall and hind legs, the pattern remained practically constant and only slight decrement was noted as distance from the heart increased.

On the basis of these findings it is concluded that certain modifications in the technique of clinical electrocardiography are desirable. The method of balanced potentials is too time-consuming for routine use. However, practically the same results can be obtained by pairing the exploring electrode with one placed over an area of slight potential variation, such as the right scapular region. Tracings should be made with the exploring electrode on the C_1 to C_6 positions inclusive and on some position at least several inches below the diaphragm. (The most favorable position will have to be determined by further study.) In certain cases it is possible that additional information may be obtained by placing the exploring electrode in the esophagus below the auricular level. The three conventional limb leads of Einthoven are not recommended. They are not merely superfluous but may be misleading.

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Editorial Note to Medical Authors: We wish to call the special attention of author-contributors and readers of this Journal to two of the most frequent errors that appear in our manuscripts.

The first—the misuse of "milligrams per cent"—is well covered on Page 53 of the American Medical Association's book entitled "Medical Writing": "Results of chemical determinations are frequently expressed as 'milligrams per cent' or 'grams per cent.' This means literally 'milligrams (or grams) per hundred milligrams (or grams),' which in most instances is not the information that the author wishes to convey. To insure accuracy a writer should specify the unit used, such as 'milligrams per hundred cubic centimeters' or 'milligrams per 100 gm.' If a number of values are (*sic*) given close together in a section or in a short paper, it usually is sufficient to supply 'per hundred cubic centimeters' the first time the phrase appears and to use merely 'milligrams' (not 'milligrams per cent') thereafter." We have become so weary of correcting this fault—and yet probably have overlooked it in many cases—that we are taking this means of trying to reduce it for the future. We hope that other journals, and especially the Journal of the American Medical Association with its large circulation, will also emphasize the point.

We should like to regard the word "consider" as indicating that the item is still under consideration or being meditated upon, *i.e.*, that no conclusion has been reached. This is usually the first meaning given by dictionaries for this word. We believe that, some dictionaries to the contrary notwithstanding, it is improper to use the word where a decision has been reached; in which case some such word as "think to be," or "regard as" or "believe to be" or "hold as an opinion" gives the more exact meaning.

THE EDITOR.